PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 May 2001 (10.05.01)	
International application No. PCT/GB00/03210	**Applicant's or agent's file reference**
International filing date (day/month/year) 21 August 2000 (21.08.00)	**Priority date** (day/month/year) 20 August 1999 (20.08.99)
Applicant STEVENS, Malcolm, Francis, Graham et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 March 2001 (16.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/GB 00/03210

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 22, no. 9, 10 May 1928 (1928-05-10) Columbus, Ohio, US; HAUSER H: "2-'Aminophenyl!benzothiazoles" page 1590; XP002154293 abstract & HELV. CHIM. ACTA, vol. 11, 1928, pages 198-209, ---	1,2,6,8
X	DE 23 33 378 A (BASF AG) 23 January 1975 (1975-01-23) the whole document, particularly page 7, examples 23 and 24 ---	1,2,6
X	DATABASE WPI Section Ch, Week 199919 Derwent Publications Ltd., London, GB; Class B02, AN 1999-226170 XP002154294 -& JP 11 060573 A (NIPPON KAYAKU KK), 2 March 1999 (1999-03-02) abstract ---	1-3,6,9
X	US 3 401 048 A (OKUBO I ET AL) 10 September 1968 (1968-09-10) the whole document, particularly example 4, starting material ---	1,2,6
X	US 3 257 204 A (SÜS O ET AL) 21 June 1966 (1966-06-21) the whole document ---	1,2,6,8
P,X	HUTCHINSON I ET AL: "The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles" TETRAHEDRON LETTERS, vol. 41, no. 3, January 2000 (2000-01), pages 425-428, XP004186279 ISSN: 0040-4039 the whole document -----	1-25

1

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB00/03210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/66 C07D277/64 C07D263/56 C07D263/57 C07F7/22
A61K31/428 A61K31/423 A61K31/555 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 06469 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 9 March 1995 (1995-03-09) cited in the application the whole document ---	1-25
X	WO 96 26932 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 6 September 1996 (1996-09-06) cited in the application the whole document --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2000	19/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 00 /03210

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11, 15, 16, 18-20 (all partly)

Present claims 1-11, 15, 16 and 18-20 relate to an extremely large number of possible compounds, their use and preparation. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and use claimed. In the present case, said claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty, in particular with regard to claims 1, 2, 6 and 8. So many documents were in fact retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) according to claim 1, wherein X is S, Q is a direct bond, R1 is halogen or trimethyltin, and n is 1, 2 or 3 (the other substituents being as indicated in claim 1), or wherein X is S, Q is a direct bond, and R5 and/or R6 is -C(Y)R7, (the other substituents being as indicated in claim 1), and the search report can only be considered as complete for the claims relating to said compounds, their use and preparation.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter...plication No
PCT/GB 00/03210

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9506469 A	09-03-1995	AT 182077 T	15-07-1999
		AU 690577 B	30-04-1998
		AU 7504994 A	22-03-1995
		CA 2170508 A	09-03-1995
		DE 69419517 D	19-08-1999
		DE 69419517 T	28-10-1999
		DK 721336 T	29-11-1999
		EP 0721336 A	17-07-1996
		ES 2133571 T	16-09-1999
		GR 3031418 T	31-01-2000
		JP 9501944 T	25-02-1997
		US 5874431 A	23-02-1999
WO 9626932 A	06-09-1996	AU 711052 B	07-10-1999
		AU 4837496 A	18-09-1996
		CA 2213737 A	06-09-1996
		EP 0812319 A	17-12-1997
		JP 11501024 T	26-01-1999
		US 6034246 A	07-03-2000
DE 2333378 A	23-01-1975	NONE	
JP 11060573 A	02-03-1999	NONE	
US 3401048 A	10-09-1968	BE 665688 A	18-10-1965
		CH 478280 B	15-09-1969
		CH 867665 A	
		DE 1291316 B	
		FR 1449758 A	24-11-1966
		GB 1125154 A	
US 3257204 A	21-06-1966	BE 581862 A	
		CH 379279 A	
		DE 1137625 B	
		FR 1238483 A	02-12-1960
		GB 895001 A	
		LU 37546 A	
		NL 126227 C	
		NL 242547 A	

PCT

PTO/PCT Rec'd 20 FEB 2002

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)*

Box No. I TITLE OF INVENTION

SUBSTITUTED 2-ARYLBENZAZOLE COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED
CAMBRIDGE HOUSE
6-10 CAMBRIDGE TERRACE
REGENT'S PARK
LONDON NW1 4JL
UNITED KINGDOM

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: UNITED KINGDOM (GB)

State *(that is, country)* of residence: UNITED KINGDOM (GB)

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

STEVENS, MALCOLM FRANCIS GRAHAM
SHEPSHED FIELDS FARMHOUSE
REMPSTONE ROAD
BELTON
LEICESTERSHIRE LE12 9XA
UNITED KINGDOM

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: UNITED KINGDOM (GB)

State *(that is, country)* of residence: UNITED KINGDOM (GB)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WILSON GUNN SKERRETT
CHARLES HOUSE
148/9 GREAT CHARLES STREET
BIRMINGHAM B3 3HT
UNITED KINGDOM

Telephone No.
+44 121 236 1038

Facsimile No.
+44 121 233 2875

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
POOLE, TRACEY DAWN
12 HATHERN CLOSE
BRIMINGTON COMMON
CHESTERFIELD S43 1PS
UNITED KINGDOM

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: UNITED KINGDOM (GB

State *(that is, country)* of residence: UNITED KINGDOM (GB)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
WESTWELL, ANDREW DAVID
189 HOWBECK ROAD
ARNOLD
NOTTINGHAM NG5 8QD
UNITED KINGDOM

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: UNITED KINGDOM (GB)

State *(that is, country)* of residence: UNITED KINGDOM (GB)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
HUTCHINSON, IAN PAUL
190 MELTON ROAD
WEST BRIDGFORD
NOTTINGHAM NG2 6FJ
UNITED KINGDOM

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: UNITED KINGDOM (GB)

State *(that is, country)* of residence: UNITED KINGDOM (GB)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
CHUA, MEI-SZE
DEPARTMENT OF MOLECULAR PHARMACOLOGY
STANFORD UNIVERSITY, SCHOOL OF MEDICINE
269 CAMPUS DRIVE, CCSR
STANFORD, CA 94305-5174,
U.S.A.

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SINGAPORE

State *(that is, country)* of residence: CA, U.S.A.

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **BZ** Belize
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **DZ** Algeria .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Sheet No. 4

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 20.08.1999	GB 9919673.5	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1 (GB 9919673.5)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 43
claims	: 8
abstract	: 1
drawings	: 2
sequence listing part of description	:
Total number of sheets	: 58

This international application is **accompanied** by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED, MALCOLM FRANCIS GRAHAM STEVENS, TRACEY DAWN POOLE, ANDREW DAVID WESTWELL, IAN PAUL HUTCHINSON AND MEI-SZE CHUA

AGENTS

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WILSON GUNN SKERRETT
Charles House
148/9 Great Charles Street
Birmingham B3 3HT
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	07.11.2001
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
JNHS/LR/P/75004.WO/B	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03210	21/08/2000	20/08/1999

Applicant
CANCER RESEARCH VENTURES LIMITED et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel.+49 89 2399-8012

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JNHS/LR/P/75004.WO/B		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03210	21/08/2000	20/08/1999
International Patent Classification (IPC) or national classification and IPC		
C07D277/66		
Applicant		
CANCER RESEARCH VENTURES LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/03/2001	07.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Johnson, C Telephone No. +49 89 2399 8287

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03210

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,3,5,6,8-35,41, 42	as originally filed			
2,4,7,36-40,43	as received on	11/10/2001	with letter of	08/10/2001

Claims, No.:

1 (part),2-11,14 (part), 17 (part),18-25	as originally filed			
12,13,14 (part)	as received on	19/03/2001	with letter of	16/03/2001
1 (part),14 (part), 15,16,17 (part)	as received on	11/10/2001	with letter of	08/10/2001

Drawings, sheets:

1/2,2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in

the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11(part),15-16(part),18-22(part),23,24-25(part).

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-11(part),15-16(part),18-22(part),24-25(part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2,6-8,11,14-16,18-24
Industrial applicability (IA)	Yes:	Claims	1-22,24-25
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III. Non-establishment of opinion

According to EPO policy, claims or parts of claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination. The examination is therefore based on the compounds of formula I which have X = S and Q = direct bond, i.e. on claims 1-11 (part), 12-14, 15-16 (part), 17, 18-25 (part).

Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

IV. Unity

In order for a group of compounds to be considered unitary, all compounds must possess the same or corresponding special technical feature (the special technical feature being that feature which distinguishes the claimed compounds from the prior art) (Rule 13.2 PCT).
In the present case, there appear to be 2 special technical features; for the claimed compounds wherein n is 1-3 it is the R^1 substituent, whereas for the compounds wherein n is 0 it is the R^5 or R^6 substituent. These 2 features are not corresponding, as they are at different positions in the molecule, and are not structurally similar. Therefore there appears to be a lack of unity.

V. Reasoned statement

Reference is made to the following documents:
D1: WO 95 06469 A
D2: WO 96 26932 A
D3: US-A-3 257 204
D4: CHEMICAL ABSTRACTS, vol. 22, no. 9, 10 May 1928 (1928-05-10) Columbus, Ohio, US; HAUSER H: '2-[Aminophenyl]benzothiazoles' page 1590; XP002154293 & HELV. CHIM. ACTA, vol. 11, 1928, pages 198-209,
D5: DATABASE WPI Section Ch, Week 199919 Derwent Publications Ltd., London, GB; Class B02, AN 1999-226170 XP002154294 -& JP 11 060573 A (NIPPON KAYAKU KK), 2 March 1999 (1999-03-02)

D6 HUTCHINSON I ET AL: 'The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles' TETRAHEDRON LETTERS, vol. 41, no. 3, January 2000 (2000-01), pages 425-428, XP004186279 ISSN: 0040-4039

Novelty

The compounds of formula (I) differ from those of D1-D6 either because of the identity of the R^1 group or because of proviso (c) in claim 1.

Claims 1-25 therefore fulfil the requirements of Article 33(2) EPC.

Inventive step

D1, D2 and D6 concern antitumour agents. The technical problem solved by the present compounds appears to be the provision of further antitumour agents.

For those compounds which have valid priority, i.e. wherein R^1 is F, D1 or D2 may be considered the closest prior art.

Those claimed compounds wherein n is 1-3 differ from the general formulae of D1 or D2 because they possess an F group instead of an alkyl, hydroxyl, alkoxy or aralkoxy group. It would not be obvious from the cited prior art that replacement of one of these prior art groups by the claimed R^1 substituent would lead to compounds which maintained the antitumour activity. Therefore the compounds wherein n is 1-3, R^1 is F and which have the alleged activity may be considered non-obvious.

Those claimed compounds wherein n is 0 differ from the general formulae of D1 or D2 because they possess a $C(Y)CH(R^8)NH_2$ substituent on the amine group. D1 discloses the possibility that the amine group may be substituted so that it forms a nitrogen-containing group convertible into an amino group (p. 3, l. 15). D2 mentions the possibility of substituting the amine by acyl derivatives such as acetyl and chloroacetyl derivatives to form active compounds with increased water solubility (p. 6 last line - p. 7 first line). However, none of the cited prior art suggests that an aminoacetyl amine substituent would be suitable for compounds with the alleged activity. Therefore those compounds wherein n is 0 and R^5 or R^6

is $C(Y)CH(R^8)NH_2$ which have the desired activity may be considered non-obvious.

For those compounds which do not claim valid priority, i.e. wherein R^1 is iodo or trimethyltin, D6 may be considered the closest prior art. It would be obvious for the skilled man wishing to solve the technical problem to modify the known antitumour compounds 7a-d. The replacement of one of the prior art substituents by a trimethyltin group would not be obvious. However, the compounds of claim 1 in which R^1 is iodo and R^5 and R^6 are hydrogen or alkyl are considered obvious modifications of the fluoro and bromo derivatives 7a-d of D6, as are their pharmaceutical compositions, medical uses and preparations.

Therefore claims 1, 2, 6-8, 11, 14-16, 18-24 do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-22, 24 and 25 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claim 23 is industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

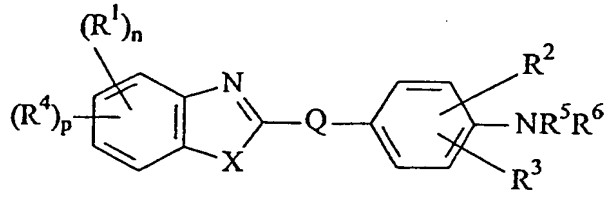
As the priority is not valid for those compounds wherein R^1 is iodo or trimethyltin, document D6, published in January 2000, is relevant prior art for the assessment of novelty and inventive step for these compounds (see section V).

VIII. Certain observations on the international application

Claims 24 and 25 contain references to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

CLAIMS

1. An arylbenzazole compound represented by the structural formula I below, or a pharmaceutically acceptable salt thereof,



(I)

wherein

X represents S or O;

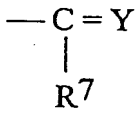
R^1 is selected from fluoro, iodo and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R^4 represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R^5 and R^6 each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R^7 represents alkyl or $-CH(R^8)NH_2$ where R^8 represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, $-CH_2-$ or –CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

subject to the following provisos:

(a) alkyl or substituted alkyl groups are linear, branched or cyclic structures but when present as linear or branched structures in the

12. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond and wherein n, R^1 and R^2 represent one of the following combinations:

n	R^1	R^2
1	4-F	3-CH_3
1	6-F	3-CH_3
1	4-F	H
1	6-F	H
2	4,5-diF	3-CH_3
2	4,6-diF	3-CH_3
2	5,7-diF	3-CH_3
1	7-F	3-CH_3
2	5,6-diF	3-CH_3
2	6,7-diF	3-CH_3
1	5-F	3-CH_3
1	5-F	H
1	4-F	3-I
1	5-F	3-I
1	6-F	3-I
1	4-F	3-Cl
1	5-F	3-Cl
1	6-F	3-Cl
1	4-F	3-Br
1	5-F	3-Br
1	6-F	3-Br

13. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, Q represents a direct bond, one of R^5 and R^6 represents H and the other represents $-C(O)CH(R^8)NH_2$, and wherein R^3 represents H, and n, R^1, R^2 and R^8 represent one of the following combinations.

n	R^1	R^2	R^8
Zero	-	H	$-CH_3$
Zero	-	3-CH_3	$-CH_3$
Zero	-	3-Cl	$-CH_3$
Zero	-	H	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-(CH_2)_4NH_2$
Zero	-	3-Cl	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-CH_2OH$
1	6-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	$-(CH_2)_4NH_2$
1	6-F	3-CH_3	$-(CH_2)_4NH_2$
1	5-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	H

14. An arylbenzazole compound which is one of the following:

4-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4-Fluoro-2-(4'-aminophenyl)benzothiazole;

6-Fluoro-2-(4'-aminophenyl)benzothiazole;

4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt;

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt; and

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole.

15. An arylbenzazole compound as claimed in any of the preceding claims for use in therapy as an active therapeutic substance characterised in that it is an acid addition salt derived from an acid selected from the group consisting of:

hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic and ethanesulphonic.

16. A compound as claimed in any one of Claims 1 to 15 for use in therapy.

17. A isotopically labelled arylbenzazole compound selected from the group consisting of 5-^{18}Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and 6-

14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JNHS/LR/P/75004.WO/B		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03210	21/08/2000	20/08/1999
International Patent Classification (IPC) or national classification and IPC C07D277/66		
Applicant CANCER RESEARCH VENTURES LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/03/2001	07.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Johnson, C Telephone No. +49 89 2399 8287

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03210

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,3,5,6,8-35,41, 42	as originally filed			
2,4,7,36-40,43	as received on	11/10/2001	with letter of	08/10/2001

Claims, No.:

1 (part),2-11,14 (part), 17 (part),18-25	as originally filed			
12,13,14 (part)	as received on	19/03/2001	with letter of	16/03/2001
1 (part),14 (part), 15,16,17 (part)	as received on	11/10/2001	with letter of	08/10/2001

Drawings, sheets:

1/2,2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in

the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:-

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11(part),15-16(part),18-22(part),23,24-25(part).

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-11(part),15-16(part),18-22(part),24-25(part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2,6-8,11,14-16,18-24
Industrial applicability (IA)	Yes:	Claims	1-22,24-25
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III. Non-establishment of opinion

According to EPO policy, claims or parts of claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination. The examination is therefore based on the compounds of formula I which have X = S and Q = direct bond, i.e. on claims 1-11 (part), 12-14, 15-16 (part), 17, 18-25 (part).

Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

IV. Unity

In order for a group of compounds to be considered unitary, all compounds must possess the same or corresponding special technical feature (the special technical feature being that feature which distinguishes the claimed compounds from the prior art) (Rule 13.2 PCT).
In the present case, there appear to be 2 special technical features; for the claimed compounds wherein n is 1-3 it is the R^1 substituent, whereas for the compounds wherein n is 0 it is the R^5 or R^6 substituent. These 2 features are not corresponding, as they are at different positions in the molecule, and are not structurally similar. Therefore there appears to be a lack of unity.

V. Reasoned statement

Reference is made to the following documents:
D1: WO 95 06469 A
D2: WO 96 26932 A
D3: US-A-3 257 204
D4: CHEMICAL ABSTRACTS, vol. 22, no. 9, 10 May 1928 (1928-05-10) Columbus, Ohio, US; HAUSER H: '2-[Aminophenyl]benzothiazoles' page 1590; XP002154293 & HELV. CHIM. ACTA, vol. 11, 1928, pages 198-209,
D5: DATABASE WPI Section Ch, Week 199919 Derwent Publications Ltd., London, GB; Class B02, AN 1999-226170 XP002154294 -& JP 11 060573 A (NIPPON KAYAKU KK), 2 March 1999 (1999-03-02)

D6 HUTCHINSON I ET AL: 'The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles' TETRAHEDRON LETTERS, vol. 41, no. 3, January 2000 (2000-01), pages 425-428, XP004186279 ISSN: 0040-4039

Novelty

The compounds of formula (I) differ from those of D1-D6 either because of the identity of the R^1 group or because of proviso (c) in claim 1.

Claims 1-25 therefore fulfil the requirements of Article 33(2) EPC.

Inventive step

D1, D2 and D6 concern antitumour agents. The technical problem solved by the present compounds appears to be the provision of further antitumour agents.

For those compounds which have valid priority, i.e. wherein R^1 is F, D1 or D2 may be considered the closest prior art.

Those claimed compounds wherein n is 1-3 differ from the general formulae of D1 or D2 because they possess an F group instead of an alkyl, hydroxyl, alkoxy or aralkoxy group. It would not be obvious from the cited prior art that replacement of one of these prior art groups by the claimed R^1 substituent would lead to compounds which maintained the antitumour activity. Therefore the compounds wherein n is 1-3, R^1 is F and which have the alleged activity may be considered non-obvious.

Those claimed compounds wherein n is 0 differ from the general formulae of D1 or D2 because they possess a $C(Y)CH(R^8)NH_2$ substituent on the amine group. D1 discloses the possibility that the amine group may be substituted so that it forms a nitrogen-containing group convertible into an amino group (p. 3, l. 15). D2 mentions the possibility of substituting the amine by acyl derivatives such as acetyl and chloroacetyl derivatives to form active compounds with increased water solubility (p. 6 last line - p. 7 first line). However, none of the cited prior art suggests that an aminoacetyl amine substituent would be suitable for compounds with the alleged activity. Therefore those compounds wherein n is 0 and R^5 or R^6

is $C(Y)CH(R^8)NH_2$ which have the desired activity may be considered non-obvious.

For those compounds which do not claim valid priority, i.e. wherein R^1 is iodo or trimethyltin, D6 may be considered the closest prior art. It would be obvious for the skilled man wishing to solve the technical problem to modify the known antitumour compounds 7a-d. The replacement of one of the prior art substituents by a trimethyltin group would not be obvious. However, the compounds of claim 1 in which R^1 is iodo and R^5 and R^6 are hydrogen or alkyl are considered obvious modifications of the fluoro and bromo derivatives 7a-d of D6, as are their pharmaceutical compositions, medical uses and preparations.

Therefore claims 1, 2, 6-8, 11, 14-16, 18-24 do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-22, 24 and 25 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claim 23 is industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

As the priority is not valid for those compounds wherein R^1 is iodo or trimethyltin, document D6, published in January 2000, is relevant prior art for the assessment of novelty and inventive step for these compounds (see section V).

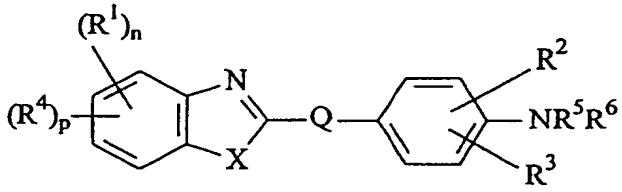
VIII. Certain observations on the international application

Claims 24 and 25 contain references to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

It has now been found that by modifying the structure of the prior art compounds their antitumour activity may be improved, whilst retaining the selectivity.

As indicated, the compounds with which the present invention is concerned include 2-arylbenzazole compounds that are of particular interest as active chemotherapeutic agents for use in therapy, especially antitumor therapy, by virtue of an ability to inhibit proliferation of certain tumor cells. Moreover, at least some of the compounds concerned are believed to be novel or new chemical entities. Furthermore, methods are provided for preparation or synthesis of the compounds, as hereinafter described. Also, in some cases the compounds are of interest as intermediates useful for the preparation of other 2-arylbenzazole compounds for use as active chemotherapeutic agents.

More particularly, according to a first aspect of the invention there is provided a compound of formula



(I)

wherein

X represents S or O;

R^1 is selected from fluoro, iodo and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

"Aryl" denotes a carbocyclic group or structure having at least one aromatic ring (e.g. phenyl) that in some cases may form part of a multiple condensed ring structure;

"Aralkyl" denotes a lower alkyl group, i.e. a cyclic, branched or straight chain alkyl group of one to six carbon atoms, in which there is an aryl substituent;

"Optionally substituted aryl" or "optionally substituted aralkyl" denotes aryl or aralkyl groups optionally substituted with one or more functional groups; and

"halo" denotes a fluorine, chlorine, bromine or iodine atom.

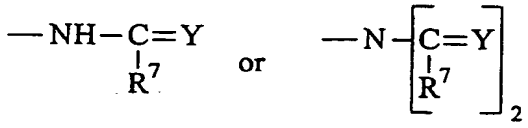
Also, the term prodrug is used in the present specification to denote modified forms or derivatives of a pharmacologically active compound which biodegrade *in vivo* and become converted into said active compound after administration, especially oral or intravenous administration, in the course of therapeutic treatment of a mammal. Such prodrugs are commonly chosen because of an enhanced solubility in aqueous media which helps to overcome formulation problems, and also in some case to give a relatively slow or controlled release of the active agent.

According to a second aspect the invention provides 2-arylbenzazole compounds as defined above for use in therapy. In this case, however, when n represents 1, 2 or 3, R^1 will usually be fluorine or iodine. The invention also provides pharmaceutical compositions comprising or containing such compounds in a form ready for administration to a mammal in need of treatment therewith.

In preferred embodiments R^1 will commonly represent F, preferably but not necessarily in the 5-position. n preferably represents 1 or 2. Also, when one

H	S	3'-Cl
H	S	3'-CN
5'-Br	S	3'-Br
5'-Cl	S	3'-Cl
5'-Me	S	3'-Cl
H	S	3'-F

Another series of benzazole compounds which provide some very promising anti-proliferative agents for use in antitumor therapy are compounds of formula (I) wherein R^1 is fluorine or iodine and the substituent NR^5R^6 is a group



wherein, as hereinbefore specified, Y represents O or S and R^7 represents the group $-CH(R^8)NH_2$ where R^8 is as previously defined.

Particular preferred compounds of formula (I) are those wherein p represents zero, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond, and wherein n, R^1 and R^2 represent one of the following combinations:

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole.

mp 280-284°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 33

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt salt **(Iai)**

The title compound is prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole and with BOC protected glycine instead of BOC protected alanine.

EXAMPLE 34

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iak)**

This was synthesised via a Jacobson cyclisation reaction from the appropriate benzanilide following the method of Route A and was separated from the 7-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 92%; mp 200-202°C; IR 3429, 3288 cm^{-1}; MS (CI) *m/z* 367.1 (M+1).

This compound can also be prepared from the appropriate 3-iodoaniline using the "Disulphide Route" previously referred to.

EXAMPLE 35

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ial)**

This was synthesised via Jacobson cyclisation, as above. It was separated from the 5-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 93%; mp 158-159°C; IR 3477, 3306 cm^{-1}; MS (CI) *m/z* 366.9 (M+1).

EXAMPLE 36

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole **(Iam)**

Acetyl Chloride (0.09g, 1.55mmol) was added to a solution of 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole (0.2g, 0.78mmol) in chloroform (5ml) containing triethylamine (86mg, 0.85mmol). The resulting solution was stirred for 30min, then poured into water (20ml). The organic layer was removed, dried (Na_2SO_4) and evaporated. Recrystallisation from ethanol gave a white solid.

Yield = 86%; mp 219-221°C; MS (CI) *m/z* 301.3 (M+1).

EXAMPLE 37

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Ian)**

5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole (5g, 0.0135mol), copper cyanide (3.65g, 0.04mol) and DMF (100ml) were heated under reflux for 6 hrs, cooled and the solvent removed under vacuum. The residue was stirred in water (50ml) for 30mins, then the product extracted with ethyl acetate (2 x 100ml). The combined extracts were dried (Na_2SO_4), evaporated and the residue recrystallised from ethanol to give a white solid.

Yield = 88%; mp 268-270°C; IR 3464, 3369, 2218 (CN) cm^{-1}; MS (CI) *m/z* 270.1 (M+1).

EXAMPLE 38

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Iao)**

This was synthesised from 4-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 18%; mp 225-227°C; IR 3471, 3366, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 39

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole (Iap)

This was synthesised from 6-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 12%; mp 258-260°C; IR 3412, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 40

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole (Iaq)

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole (1g, 3.75mmol) was dissolved in 80% sulfuric acid (50ml) and heated at 100°C for 2 hrs. After cooling, the reaction mixture was diluted with water (100ml) and the pH adjusted to 7.5 using 50% sodium hydroxide. The product was extracted with ethyl acetate (3 x 50ml), the extracts dried (Na_2SO_4) and evaporated to leave a yellow solid which was taken up in THF (20ml) and added dropwise to a solution of $LiAlH_4$ (0.7g, 0.019mol) in THF (15ml). After stirring at 25°C for 2 hrs, water (20ml) was added and the product extracted with ethyl acetate (3 x 50ml). The organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (10% ethyl acetate /dichloromethane) to leave a yellow powder.

Yield = 34%; mp 242-245°C; IR 3379, 3333, 1448cm^{-1}; MS (CI) *m/z* 275.1 (M+1).

EXAMPLE 41

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt (Iar)

Synthesised by same method as 5-fluoro analogue (Iaf).

Yield = 96%; mp 268-270°C; MS (CI) *m/z* 348.0 (M+1).

EXAMPLE 42

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride (**Ias**)

Synthesised by same method as 5-fluoro analogue **(Iad)**.

Yield = 74%; mp 278-281°C; MS (CI) *m/z* 405.0 (M+1).

EXAMPLE 43

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole (**Iat**)

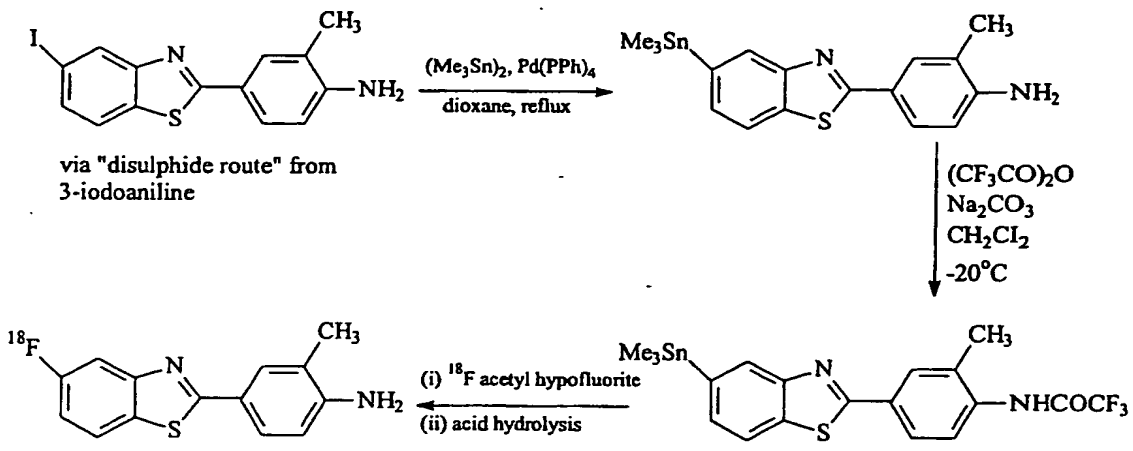
5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole (Compound **Iak**) (1.4g, 4.12mmol) and tetrakis triphenylphosphine palladium (48mg, 0.41mmol) were dissolved in dioxane (20ml) and placed under nitrogen. Hexamethylditin (5g, 0.15mol) was added and the resulting solution heated under reflux for 4hrs. The precipitated palladium was filtered from solution and washed with ethyl acetate (50ml). The organic fractions were evaporated and chromatographed (chloroform) to leave a white waxy solid. Recrystallisation from ethanol gave clear needles.

Yield = 85%; mp 158-160°C; MS (CI) *m/z* 402.8, 403.4, 404.9, 405.5 (M+1).

EXAMPLE 44

5-^{18}Fluoro-2-(4'-amino-3'-methylbenzothiazole)

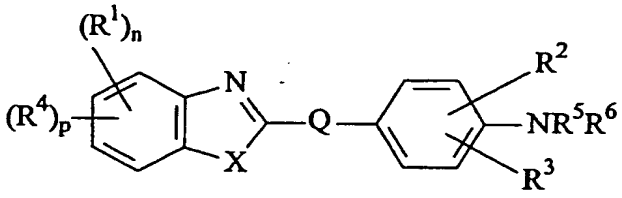
The compound **Iat** of Example 44 can be used as an intermediate in the preparation of the above ^{18}F labelled 5-fluoro compound from the corresponding 5-iodo substituted compound mentioned earlier. In this case the compound **Iat** is reacted at -20°C with $(CF_3CO)_2O$ in the presence of Na_2CO_3 and CH_2Cl_2 to form the trifluoroacetyl derivative which is then converted into the title compound by reacting with ^{18}F acetyl hypofluorite followed by acid hydrolysis. The overall scheme is depicted in the diagram below.



Of the compounds described above, the compound 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **Ik** and its lysyl amino acid amide prodrug **Iad**, in the form for instance of its water soluble dihydrochloride salt prepared as in Example 30 from its parent compound, are of especial interest for clinical use as effective antitumour agents. The solubility of this particular prodrug **Iad** in water and its chemical robustness makes it very suitable for parenteral administration as an injectable formulation, sterilised by filtration, after which it becomes converted *in vivo* to the 5-fluoro substituted compound **Ik**.

TABLE 1

In vitro activity (IC_{50} concentration in nM) of various compounds of Formula (I)



(I)

wherein

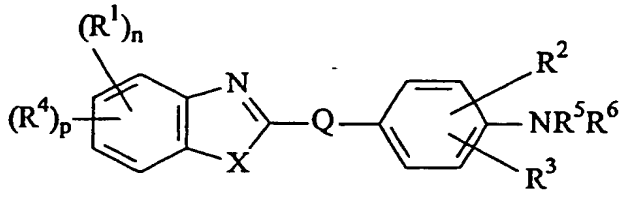
p = O, X = S, Q is a direct bond, R^3 = H, Y = O, R^7 = -CH(R^8)NH_3Cl

n	R^1	R^2	R^5	R^6	R^8	IC_{50} in MCF-7	IC_{50} in MDA468	Compound of formula
1	4-F	3-CH_3	H	H		<0.1	0.13	**Ia**
1	6-F	3-CH_3	H	H		<0.1	0.11	**Ib**
1	4-F	H	H	H		8.54	29.4	**Ic**
1	6-F	H	H	H		<0.1	48.1	**Id**
2	4,5-diF	3-CH_3	H	H		0.64	0.67	**Ie**
2	4,6-diF	3-CH_3	H	H		<0.1	5.35	**If**
2	5,7-diF	3-CH_3	H	H		0.9	4.4	**Ig**
1	7-F	3-CH_3	H	H		2.39	10.35	**Ih**
2	5,6-diF	3-CH_3	H	H		<0.1	3.55	**Ii**
1	5-F	3-CH_3	H	H		<0.1	<0.1	**Ik**
1	5-F	H	H	H		<0.1	<0.1	**Il**
1	4-F	3-I	H	H		7.88	9.11	**Im**
1	5-F	3-I	H	H		<0.1	<0.1	**In**
1	6-F	3-I	H	H		<0.1	<0.1	**Io**
1	4-F	3-Cl	H	H		0.95	1.93	**Ip**
1	5-F	3-Cl	H	H		7.09	18.9	**Iq**
1	6-F	3-Cl	H	H		4.08	11.7	**Ir**
1	4-F	3-Br	H	H		38.2	24	**Is**
1	5-F	3-Br	H	H		<0.1	0.2	**It**
1	6-F	3-Br	H	H		45.5	68.7	**Iu**
1	5-I	3-CH_3	H	H		492.96	80.86*	**Iak**
1	7-I	3-CH_3	H	H		28.28	323.11	**Ial**
1	5-F	3-CH_3	H	$COCH_3$		7.64*	5.84*	**Iam**
1	5-F	3-CN	H	H		<0.1	<0.1	**Ian**
1	5-F	3-CH_2OH	H	H		<0.1	0.43	**Iaq**
0		3-F	H	H		1.58	33.41	
0		H	H	C(Y)R^7	CH_3	60	40	**Iv**
0		3-CH_3	H	C(Y)R^7	CH_3	360	340	**Iw**
0		3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	80	70	**Iz**
1	6-F	3-CH_3	H	C(Y)R^7	CH_3	44	297	**Iac**
1	5-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	40	158	**Iad**
1	6-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	147.31	328.09	**Iae**
1	5-F	3-CH_3	H	C(Y)R^7	CH_3	5.89	37.74	**Iaf**
2	5,6-diF	3-CH_3	H	C(Y)R^7	CH_3	33.06	216.9	**Iar**
2	5,6-diF	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	30.69	301.87	**Ias**

* IC_{50} concentration in μM

CLAIMS

1. An arylbenzazole compound represented by the structural formula I below, or a pharmaceutically acceptable salt thereof,



(I)

wherein

X represents S or O;

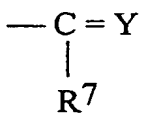
R^1 is selected from fluoro, iodo and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R^4 represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R^5 and R^6 each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R^7 represents alkyl or $-CH(R^8)NH_2$ where R^8 represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, $-CH_2-$ or –CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

subject to the following provisos:

(a) alkyl or substituted alkyl groups are linear, branched or cyclic structures but when present as linear or branched structures in the

12. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond and wherein n, R^1 and R^2 represent one of the following combinations:

n	R^1	R^2
1	4-F	3-CH_3
1	6-F	3-CH_3
1	4-F	H
1	6-F	H
2	4,5-diF	3-CH_3
2	4,6-diF	3-CH_3
2	5,7-diF	3-CH_3
1	7-F	3-CH_3
2	5,6-diF	3-CH_3
2	6,7-diF	3-CH_3
1	5-F	3-CH_3
1	5-F	H
1	4-F	3-I
1	5-F	3-I
1	6-F	3-I
1	4-F	3-Cl
1	5-F	3-Cl
1	6-F	3-Cl
1	4-F	3-Br
1	5-F	3-Br
1	6-F	3-Br

13. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, Q represents a direct bond, one of R^5 and R^6 represents H and the other represents $-C(O)CH(R^8)NH_2$, and wherein R^3 represents H, and n, R^1, R^2 and R^8 represent one of the following combinations.

n	R^1	R^2	R^8
Zero	-	H	$-CH_3$
Zero	-	3-CH_3	$-CH_3$
Zero	-	3-Cl	$-CH_3$
Zero	-	H	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-(CH_2)_4NH_2$
Zero	-	3-Cl	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-CH_2OH$
1	6-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	$-(CH_2)_4NH_2$
1	6-F	3-CH_3	$-(CH_2)_4NH_2$
1	5-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	H

14. An arylbenzazole compound which is one of the following:

4-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4-Fluoro-2-(4'-aminophenyl)benzothiazole;

6-Fluoro-2-(4'-aminophenyl)benzothiazole;

4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt;

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt; and

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole.

15. An arylbenzazole compound as claimed in any of the preceding claims for use in therapy as an active therapeutic substance characterised in that it is an acid addition salt derived from an acid selected from the group consisting of:

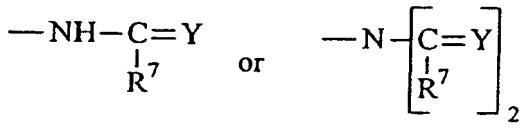
hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic and ethanesulphonic.

16. A compound as claimed in any one of Claims 1 to 15 for use in therapy.

17. A isotopically labelled arylbenzazole compound selected from the group consisting of 5-^{18}Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and 6-

H	S	3'-Cl
H	S	3'-CN
5'-Br	S	3'-Br
5'-Cl	S	3'-Cl
5'-Me	S	3'-Cl
H	S	3'-F

Another series of benzazole compounds which provide some very promising anti-proliferative agents for use in antitumor therapy are compounds of formula (I) wherein R^1 is fluorine or other halogen or CF_3 and the substituent NR^5R^6 is a group



wherein, as hereinbefore specified, Y represents O or S and R^7 represents the group $-CH(R^8)NH_2$ where R^8 is as previously defined.

Particular preferred compounds of formula (I) are those wherein p represents zero, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond, and wherein n, R^1 and R^2 represent one of the following combinations:

"Aryl" denotes a carbocyclic group or structure having at least one aromatic ring (e.g. phenyl) that in some cases may form part of a multiple condensed ring structure;

"Aralkyl" denotes a lower alkyl group, i.e. a cyclic, branched or straight chain alkyl group of one to six carbon atoms, in which there is an aryl substituent;

"Optionally substituted aryl" or "optionally substituted aralkyl" denotes aryl or aralkyl groups optionally substituted with one or more functional groups; and

"halo" denotes a fluorine, chlorine, bromine or iodine atom.

Also, the term prodrug is used in the present specification to denote modified forms or derivatives of a pharmacologically active compound which biodegrade *in vivo* and become converted into said active compound after administration, especially oral or intravenous administration, in the course of therapeutic treatment of a mammal. Such prodrugs are commonly chosen because of an enhanced solubility in aqueous media which helps to overcome formulation problems, and also in some case to give a relatively slow or controlled release of the active agent.

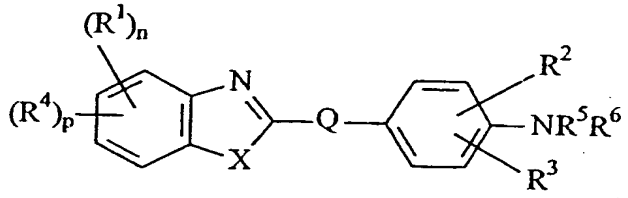
According to a second aspect the invention provides 2-arylbenzazole compounds as defined above for use in therapy. In this case, however, when n represents 1, 2 or 3, R^1 will usually be halogen or CF_3. The invention also provides pharmaceutical compositions comprising or containing such compounds in a form ready for administration to a mammal in need of treatment therewith.

In preferred embodiments R^1 will commonly represent F, preferably but not necessarily in the 5-position. n preferably represents 1 or 2. Also, when one

It has now been found that by modifying the structure of the prior art compounds their antitumour activity may be improved, whilst retaining the selectivity.

As indicated, the compounds with which the present invention is concerned include 2-arylbenzazole compounds that are of particular interest as active chemotherapeutic agents for use in therapy, especially antitumor therapy, by virtue of an ability to inhibit proliferation of certain tumor cells. Moreover, at least some of the compounds concerned are believed to be novel or new chemical entities. Furthermore, methods are provided for preparation or synthesis of the compounds, as hereinafter described. Also, in some cases the compounds are of interest as intermediates useful for the preparation of other 2-arylbenzazole compounds for use as active chemotherapeutic agents.

More particularly, according to a first aspect of the invention there is provided a compound of formula



(I)

wherein

X represents S or O;

R^1 is selected from halogen, CF_3 and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole.

mp 280-284°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 33

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt salt **(Iai)**

The title compound is prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole and with BOC protected glycine instead of BOC protected alanine.

EXAMPLE 34

5-Bromo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iaj)**

Synthesis is analogous to that of 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ik)** as described in Example 11 but starting with 5-bromo-2-(4'-amino-3'-methylphenyl)benzothiazole.

Yield = 75%; mp 224-227°C; IR 3465, 3342 cm^{-1}; MS (CI) *m/z* 318.9, 320.6 (M+1).

EXAMPLE 35

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iak)**

This was synthesised via a Jacobson cyclisation reaction from the appropriate benzanilide following the method of Route A and was separated from the 7-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 92%; mp 200-202°C; IR 3429, 3288 cm^{-1}; MS (CI) *m/z* 367.1 (M+1).

This compound can also be prepared from the appropriate 3-iodoaniline using the "Disulphide Route" previously referred to.

EXAMPLE 36

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ial)**

This was synthesised via Jacobson cyclisation, as above. It was separated from the 5-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 93%; mp 158-159°C; IR 3477, 3306 cm^{-1}; MS (CI) *m/z* 366.9 (M+1).

EXAMPLE 37

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole **(Iam)**

Acetyl Chloride (0.09g, 1.55mmol) was added to a solution of 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole (0.2g, 0.78mmol) in chloroform (5ml) containing triethylamine (86mg, 0.85mmol). The resulting solution was stirred for 30min, then poured into water (20ml). The organic layer was removed, dried (Na_2SO_4) and evaporated. Recrystallisation from ethanol gave a white solid.

Yield = 86%; mp 219-221°C; MS (CI) *m/z* 301.3 (M+1).

EXAMPLE 38

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Ian)**

5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole (5g, 0.0135mol), copper cyanide (3.65g, 0.04mol) and DMF (100ml) were heated under reflux for 6 hrs, cooled and the solvent removed under vacuum. The residue was stirred in water (50ml) for 30mins, then the product extracted with ethyl acetate (2 x 100ml). The combined extracts were dried (Na_2SO_4), evaporated and the residue recrystallised from ethanol to give a white solid.

Yield = 88%; mp 268-270°C; IR 3464, 3369, 2218 (CN) cm^{-1}; MS (CI) *m/z* 270.1 (M+1).

EXAMPLE 39

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Iao)**

This was synthesised from 4-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 18%; mp 225-227°C; IR 3471, 3366, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 40

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Iap)**

This was synthesised from 6-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 12%; mp 258-260°C; IR 3412, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 41

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole **(Iaq)**

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole (1g, 3.75mmol) was dissolved in 80% sulfuric acid (50ml) and heated at 100°C for 2 hrs. After cooling, the reaction mixture was diluted with water (100ml) and the pH adjusted to 7.5 using 50% sodium hydroxide. The product was extracted with ethyl acetate (3 x 50ml), the extracts dried (Na_2SO_4) and evaporated to leave a yellow solid which was taken up in THF (20ml) and added dropwise to a solution of $LiAlH_4$ (0.7g, 0.019mol) in THF (15ml). After stirring at 25°C for 2 hrs, water (20ml) was added and the product extracted with ethyl acetate (3 x

50ml). The organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (10% ethyl acetate /dichloromethane) to leave a yellow powder.

Yield = 34%; mp 242-245°C; IR 3379, 3333, 1448cm^{-1}; MS (CI) *m/z* 275.1 (M+1).

EXAMPLE 42

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt **(Iar)**

Synthesised by same method as 5-fluoro analogue **(Iaf)**.

Yield = 96%; mp 268-270°C; MS (CI) *m/z* 348.0 (M+1).

EXAMPLE 43

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride **(Ias)**

Synthesised by same method as 5-fluoro analogue **(Iad)**.

Yield = 74%; mp 278-281°C; MS (CI) *m/z* 405.0 (M+1).

EXAMPLE 44

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iat)**

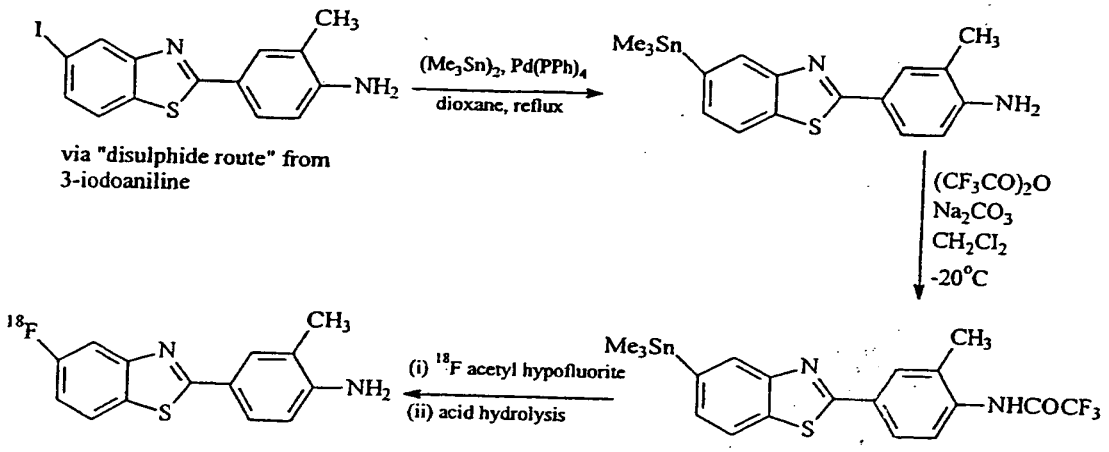
5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole (Compound **Iak**) (1.4g, 4.12mmol) and tetrakis triphenylphosphine palladium (48mg, 0.41mmol) were dissolved in dioxane (20ml) and placed under nitrogen. Hexamethylditin (5g, 0.15mol) was added and the resulting solution heated under reflux for 4hrs. The precipitated palladium was filtered from solution and washed with ethyl acetate (50ml). The organic fractions were evaporated and chromatographed (chloroform) to leave a white waxy solid. Recrystallisation from ethanol gave clear needles.

Yield = 85%; mp 158-160°C; MS (CI) *m/z* 402.8, 403.4, 404.9, 405.5 (M+1).

EXAMPLE 45

5-^{18}Fluoro-2-(4'-amino-3'-methylbenzothiazole)

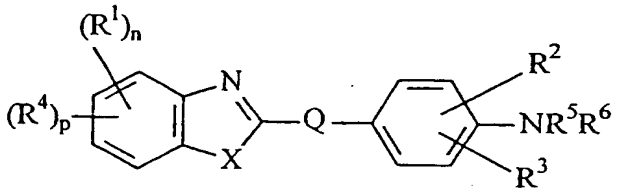
The compound **Iat** of Example 44 can be used as an intermediate in the preparation of the above ^{18}F labelled 5-fluoro compound from the corresponding 5-iodo substituted compound mentioned earlier. In this case the compound **Iat** is reacted at -20°C with $(CF_3CO)_2O$ in the presence of Na_2CO_3 and CH_2Cl_2 to form the trifluoroacetyl derivative which is then converted into the title compound by reacting with ^{18}F acetyl hypofluorite followed by acid hydrolysis. The overall scheme is depicted in the diagram below.



Of the compounds described above, the compound 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **Ik** and its lysyl amino acid amide prodrug **Iad**, in the form for instance of its water soluble dihydrochloride salt prepared as in Example 30 from its parent compound, are of especial interest for clinical use as effective antitumour agents. The solubility of this particular prodrug **Iad** in water and its chemical robustness makes it very suitable for parenteral administration as an injectable formulation, sterilised by filtration, after which it becomes converted *in vivo* to the 5-fluoro substituted compound **Ik**.

TABLE 1

In vitro activity (IC_{50} concentration in nM) of various compounds of Formula (I)



(I)

wherein

p = O, X = S, Q is a direct bond, R^3 = H, Y = O, R^7 = -CH(R^8)NH_3Cl

n	R^1	R^2	R^5	R^6	R^8	IC_{50} in MCF-7	IC_{50} in MDA468	Compound of formula
1	4-F	3-CH_3	H	H		<0.1	0.13	**Ia**
1	6-F	3-CH_3	H	H		<0.1	0.11	**Ib**
1	4-F	H	H	H		8.54	29.4	**Ic**
1	6-F	H	H	H		<0.1	48.1	**Id**
2	4,5-diF	3-CH_3	H	H		0.64	0.67	**Ie**
2	4,6-diF	3-CH_3	H	H		<0.1	5.35	**If**
2	5,7-diF	3-CH_3	H	H		0.9	4.4	**Ig**
1	7-F	3-CH_3	H	H		2.39	10.35	**Ih**
2	5,6-diF	3-CH_3	H	H		<0.1	3.55	**Ii**
1	5-F	3-CH_3	H	H		<0.1	<0.1	**Ik**
1	5-F	H	H	H		<0.1	<0.1	**Il**
1	4-F	3-I	H	H		7.88	9.11	**Im**
1	5-F	3-I	H	H		<0.1	<0.1	**In**
1	6-F	3-I	H	H		<0.1	<0.1	**Io**
1	4-F	3-Cl	H	H		0.95	1.93	**Ip**
1	5-F	3-Cl	H	H		7.09	18.9	**Iq**
1	6-F	3-Cl	H	H		4.08	11.7	**Ir**
1	4-F	3-Br	H	H		38.2	24	**Is**
1	5-F	3-Br	H	H		<0.1	0.2	**It**
1	6-F	3-Br	H	H		45.5	68.7	**Iu**
1	5-Br	3-CH_3	H	H		4.02		**Iaj**
1	5-I	3-CH_3	H	H		492.96	80.86*	**Iak**
1	7-I	3-CH_3	H	H		28.28	323.11	**Ial**
1	5-F	3-CH_3	H	$COCH_3$		7.64*	5.84*	**Iam**
1	5-F	3-CN	H	H		<0.1	<0.1	**Ian**
1	5-F	3-CH_2OH	H	H		<0.1	0.43	**Iaq**
0		3-F	H	H		1.58	33.41	
0		H	H	C(Y)R^7	CH_3	60	40	**Iv**
0		3-CH_3	H	C(Y)R^7	CH_3	360	340	**Iw**
0		3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	80	70	**Iz**
1	6-F	3-CH_3	H	C(Y)R^7	CH_3	44	297	**Iac**
1	5-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	40	158	**Iad**
1	6-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	147.31	328.09	**Iae**
1	5-F	3-CH_3	H	C(Y)R^7	CH_3	5.89	37.74	**Iaf**
2	5,6-diF	3-CH_3	H	C(Y)R^7	CH_3	33.06	216.9	**Iar**
2	5.6-diF	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	30.69	301.87	**Ias**

* IC_{50} concentration in μM

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/03210	International filing date *(day/month/year)* 21/08/2000	(Earliest) Priority Date *(day/month/year)* 20/08/1999
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   SUBSTITUTED 2-ARYLBENZAZOLE COMPOUNDS AND THEIR USE AS ANTITUMOUR AGENTS

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. =

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11, 15, 16, 18-20 (all partly)

Present claims 1-11, 15, 16 and 18-20 relate to an extremely large number of possible compounds, their use and preparation. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and use claimed. In the present case, said claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty, in particular with regard to claims 1, 2, 6 and 8. So many documents were in fact retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) according to claim 1, wherein X is S, Q is a direct bond, R1 is halogen or trimethyltin, and n is 1, 2 or 3 (the other substituents being as indicated in claim 1), or wherein X is S, Q is a direct bond, and R5 and/or R6 is -C(Y)R7, (the other substituents being as indicated in claim 1), and the search report can only be considered as complete for the claims relating to said compounds, their use and preparation.

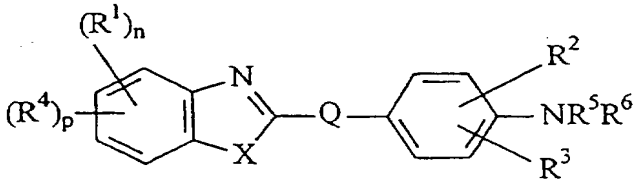
The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03210

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Substituted 2-phenylbenzazole compounds of formula (I) wherein X represents S or O and Q represents a direct bond, -CH2-or-CH=CH-, exhibit selective antiproliferative activity in respect of mammalian tumour cells. At least in preferred embodiments the benzene ring of the benzazole nucleus has a halogen substituent, preferably fluorine, and the 2-phenyl group has a 4'-amino substituent which may be conjugated with an amino acid to provide a water soluble amino acid amide prodrug or salt thereof.



(I)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/GB 00/03210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/66 C07D277/64 C07D263/56 C07D263/57 C07F7/22
A61K31/428 A61K31/423 A61K31/555 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 06469 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 9 March 1995 (1995-03-09) cited in the application the whole document ---	1-25
X	WO 96 26932 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 6 September 1996 (1996-09-06) cited in the application the whole document --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2000	19/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X A3 A3a	CHEMICAL ABSTRACTS, vol. 22, no. 9, 10 May 1928 (1928-05-10) Columbus, Ohio, US; HAUSER H: "2-'Aminophenyl!benzothiazoles" page 1590; XP002154293 abstract & HELV. CHIM. ACTA, vol. 11, 1928, pages 198-209,	1,2,6,8
X A4	DE 23 33 378 A (BASF AG) 23 January 1975 (1975-01-23) the whole document, particularly page 7, examples 23 and 24	1,2,6
X A5 A5a	DATABASE WPI Section Ch, Week 199919 Derwent Publications Ltd., London, GB; Class B02, AN 1999-226170 XP002154294 -& JP 11 060573 A (NIPPON KAYAKU KK), 2 March 1999 (1999-03-02) abstract	1-3,6,9
X A6	US 3 401 048 A (OKUBO I ET AL) 10 September 1968 (1968-09-10) the whole document, particularly example 4, starting material	1,2,6
X A7	US 3 257 204 A (SÜS O ET AL) 21 June 1966 (1966-06-21) the whole document	1,2,6,8
P,X A8	HUTCHINSON I ET AL: "The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles" TETRAHEDRON LETTERS, vol. 41, no. 3, January 2000 (2000-01), pages 425-428, XP004186279 ISSN: 0040-4039 the whole document	1-25

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14354 A1

(51) International Patent Classification[7]: C07D 277/66, 277/64, 263/56, 263/57, C07F 7/22, A61K 31/428, 31/423, 31/555, A61P 35/00

(21) International Application Number: PCT/GB00/03210

(22) International Filing Date: 21 August 2000 (21.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9919673.5 20 August 1999 (20.08.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

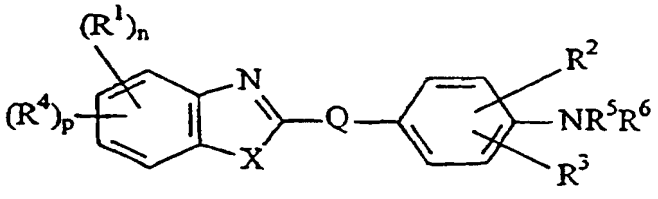
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/14354 A1

(54) Title: SUBSTITUTED 2-ARYLBENZAZOLE COMPOUNDS AND THEIR USE AS ANTITUMOUR AGENTS



(I)

(57) Abstract: Substituted 2-phenylbenzazole compounds of formula (I) wherein X represents S or O and Q represents a direct bond, -CH2- or -CH=CH-, exhibit selective antiproliferative activity in respect of mammalian tumour cells. At least in preferred embodiments the benzene ring of the benzazole nucleus has a halogen substituent, preferably fluorine, and the 2-phenyl group has a 4'-amino substituent which may be conjugated with an amino acid to provide a water soluble amino acid amide prodrug or salt thereof.

SUBSTITUTED 2-ARYLBENZAZOLE COMPOUNDS AND THEIR USE AS ANTITUMOUR AGENTS

Field of the Invention

The present invention relates to 2-arylbenzazole compounds. It is particularly concerned with such 2-arylbenzazole compounds which are biologically active, especially in respect of an ability selectively to inhibit proliferation of certain mammalian tumor cells. The invention is also concerned with compositions containing such 2-arylbenzazole compounds for use in therapy, especially antitumour therapy, and with the preparation thereof. In addition, the invention provides 2-arylbenzazole compounds which represent useful new chemical entities.

Background and Summary of the Invention

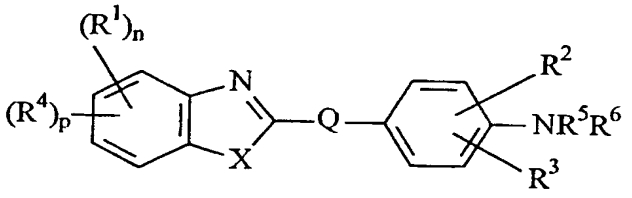
Various 2-arylbenzazole compounds found to be active in inhibiting proliferation of certain tumor cells and exemplified by 2-(4'-aminophenyl)benzothiazole and close analogues or acid addition salts thereof are disclosed in PCT international patent publications WO 95/06469 and WO 96/26932.

For some of the benzazole compounds disclosed in WO 95/06469, for instance the compound 2-(4'-aminophenyl)benzothiazole which has been designated the reference code CJM 126, a remarkably high specific inhibitory activity has been found in respect of certain human breast cancer cell lines. In WO 96/26932 compounds such as 2-(4'-amino-3'-methylphenyl)benzothiazole (reference code DF203) for example have been disclosed that exhibit anti-proliferative activity selectively in respect of a number of different cell lines that relate to a range of various mammalian cancers other than human breast cancer.

It has now been found that by modifying the structure of the prior art compounds their antitumour activity may be improved, whilst retaining the selectivity.

As indicated, the compounds with which the present invention is concerned include 2-arylbenzazole compounds that are of particular interest as active chemotherapeutic agents for use in therapy, especially antitumor therapy, by virtue of an ability to inhibit proliferation of certain tumor cells. Moreover, at least some of the compounds concerned are believed to be novel or new chemical entities. Furthermore, methods are provided for preparation or synthesis of the compounds, as hereinafter described. Also, in some cases the compounds are of interest as intermediates useful for the preparation of other 2-arylbenzazole compounds for use as active chemotherapeutic agents.

More particularly, according to a first aspect of the invention there is provided a compound of formula



(I)

wherein

X represents S or O;

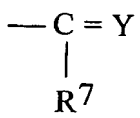
R^1 is selected from halogen, CF_3 and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R^4 represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R^5 and R^6 each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R^7 represents alkyl or $-CH(R^8)NH_2$ where R^8 represents hydrogen or an optionally substituted alkyl such as a hydroxyalkyl or amino alkyl for example ;

Q represents a direct bond, $-CH_2-$ or –CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

or a prodrug and/or a pharmaceutically acceptable salt thereof;

subject to the following provisos:

(a) alkyl or substituted alkyl groups are linear, branched or cyclic structures but when present as linear or branched structures in the compound or as a moiety in another group such as alkoxy they are composed of less then ten carbon atoms, and preferably of less than 6 carbon atoms.

(b) p represents zero or 1 when n represents 3;

(c) when n represents zero, R^5 or R^6 represents $-C(Y)-CH(R^8)NH_2$;

(d) where a group is optionally substituted, unless otherwise specified the or each substituent is selected from halogen, OH, SH, NH_2, COOH and $CONH_2$;

In this specification the following definitions apply in respect of certain terms used herein:

"Aryl" denotes a carbocyclic group or structure having at least one aromatic ring (e.g. phenyl) that in some cases may form part of a multiple condensed ring structure;

"Aralkyl" denotes a lower alkyl group, i.e. a cyclic, branched or straight chain alkyl group of one to six carbon atoms, in which there is an aryl substituent;

"Optionally substituted aryl" or "optionally substituted aralkyl" denotes aryl or aralkyl groups optionally substituted with one or more functional groups; and

"halo" denotes a fluorine, chlorine, bromine or iodine atom.

Also, the term prodrug is used in the present specification to denote modified forms or derivatives of a pharmacologically active compound which biodegrade *in vivo* and become converted into said active compound after administration, especially oral or intravenous administration, in the course of therapeutic treatment of a mammal. Such prodrugs are commonly chosen because of an enhanced solubility in aqueous media which helps to overcome formulation problems, and also in some case to give a relatively slow or controlled release of the active agent.

According to a second aspect the invention provides 2-arylbenzazole compounds as defined above for use in therapy. In this case, however, when n represents 1, 2 or 3, R^1 will usually be halogen or CF_3. The invention also provides pharmaceutical compositions comprising or containing such compounds in a form ready for administration to a mammal in need of treatment therewith.

In preferred embodiments R^1 will commonly represent F, preferably but not necessarily in the 5-position. n preferably represents 1 or 2. Also, when one

of R^5 and R^6 represents $-C(Y)-CH(R^8)NH_2$, the other preferably represents hydrogen.

Fluorine substituted compounds of the invention may incorporate the isotope ^{18}F. Such ^{18}F-substituted compounds provide a further aspect of the invention and are of use for imaging purposes, for example as positron emitting tracers for use in positron emission tomography (PET). By administering a small amount of such ^{18}F-substituted compounds followed by carrying out positron emission tomography in accordance with known techniques, preliminary tests may be carried out to assess the effectiveness of such compounds against a particular tumour in a patient under investigation, or to diagnose the presence of a suspected tumour using an ^{18}F containing compound of known antitumour efficacy.

One particular ^{18}F labelled compound useful as a tracer for positron emission tomography in tumour diagnostic studies is 5- or 6- ^{18}Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and amino acid conjugated prodrug forms and/or salts thereof. This may be conveniently prepared from the corresponding 5- or 6-iodo substituted compound as hereinafter described.

Preferred compounds of formula (I) wherein p represents 1 include compounds in which R^4 represents alkyl, alkoxy or benzyloxy. Alkyl, however, may be substituted by halogen or by hydroxy. It is also usually preferred that X represents sulphur.

Preferred compounds of formula (I) may also be further characterised by at least one of the following features:

(a) at least some alkyl groups when present as such or as a moiety in other groups such as alkoxy are methyl or ethyl;

(b) where a substituent represents or incorporates halogen, such halogen is selected from fluorine, iodine, bromine and chlorine.

A suitable prodrug of a compound of formula **(I)** is an amino acid amide which may be formed by conjugating the compound with the amino acid in question, e.g. alanine, lysine or serine. Thus R^5 or R^6 optionally represents $-C(O)-CH(R^8)NH_2$ or a salt thereof. Examples of suitable substituents for R^8 to represent include hydrogen, $-CH_3$, $-(CH_2)_4NH_2$ or $-CH_2OH$. The stereochemistry of the R^5 or R^6 substituent is either D or L or it is a racemic mixture. The L-stereoisomer is generally preferred.

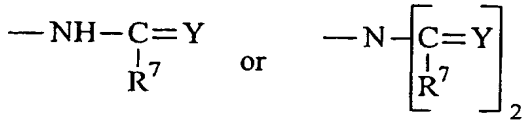
It has been found that at least for compounds of formula **(I)** wherein R^5 and R^6 both represent hydrogen, i.e. wherein the phenyl group has a 4'-NH_2 substituent, a very effective degree of anti-proliferative activity against various mammalian tumor cells may arise when R^2 represents a halogen atom, or represents a C_1-C_5 lower alkyl group (preferably Me or Et), in the 3' position of the phenyl group. For example, the particular combinations of 4'-NH_2 and 3'-F, 4'-NH_2 and 3'-Cl, 4'-NH_2 and 3'-Br, 4'-NH_2 and 3'-I, 4'-NH_2 and 3'-Me, and 4'-NH_2 and 3'-Et in the phenyl group of the 2-aryl component have been found to yield compounds with potent anti-proliferative properties against at least some selected tumor cells. The 3' position substituent may alternatively be substituted by a cyano group, giving a further combination 4'-NH_2 and 3'-CN.

Compounds of formula **(I)** wherein R^2 is a 3'-substituent in the phenyl group, and which are of particular interest, include those compounds where p represents zero, R^5 and R^6 both represent hydrogen, and the combination of substituents R^3, X and R^2 is selected from one of the following combinations:

R^3	X	R^2
H	S	3'-Me
H	S	3'-Et
H	O	3'-I
H	S	3'-Br

H	S	3'-Cl
H	S	3'-CN
5'-Br	S	3'-Br
5'-Cl	S	3'-Cl
5'-Me	S	3'-Cl
H	S	3'-F

Another series of benzazole compounds which provide some very promising anti-proliferative agents for use in antitumor therapy are compounds of formula **(I)** wherein R^1 is fluorine or other halogen or CF_3 and the substituent NR^5R^6 is a group



wherein, as hereinbefore specified, Y represents O or S and R^7 represents the group $-CH(R^8)NH_2$ where R^8 is as previously defined.

Particular preferred compounds of formula **(I)** are those wherein p represents zero, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond, and wherein n, R^1 and R^2 represent one of the following combinations:

n	R^1	R^2	Compound of formula
1	4-F	3-CH_3	**(Ia)**
1	6-F	3-CH_3	**(Ib)**
1	4-F	H	**(Ic)**
1	6-F	H	**(Id)**
2	4,5-diF	3-CH_3	**(Ie)**
2	4,6-diF	3-CH_3	**(If)**
2	5,7-diF	3-CH_3	**(Ig)**
1	7-F	3-CH_3	**(Ih)**
2	5,6-diF	3-CH_3	**(Ii)**
2	6,7-diF	3-CH_3	**(Ij)**
1	5-F	3-CH_3	**(Ik)**
1	5-F	H	**(Il)**
1	4-F	3-I	**(Im)**
1	5-F	3-I	**(In)**
1	6-F	3-I	**(Io)**
1	4-F	3-Cl	**(Ip)**
1	5-F	3-Cl	**(Iq)**
1	6-F	3-Cl	**(Ir)**
1	4-F	3-Br	**(Is)**
1	5-F	3-Br	**(It)**
1	6-F	3-Br	**(Iu)**

A further particularly preferred compound is a compound of formula **(I)** wherein p represents zero, X represents S, Q represents a direct bond, one of R^5 and R^6 represents H and the other represents $-C(Y)R^7$ wherein Y represents O and R^7 represents $-CH(R^8)NH_2$, and wherein R^3 represents H, and n, R^1, R^2 and R^8 represent one of the following combinations:

n	R^1	R^2	R^8	Compound of formula
Zero	-	H	$-CH_3$	**(Iv)**
Zero	-	3-CH_3	$-CH_3$	**(Iw)**
Zero	-	3-Cl	$-CH_3$	**(Ix)**
Zero	-	H	$-(CH_2)_4NH_2$	**(Iy)**
Zero	-	3-CH_3	$-(CH_2)_4NH_2$	**(Iz)**
Zero	-	3-Cl	$-(CH_2)_4NH_2$	**(Iaa)**
Zero	-	3-CH_3	$-CH_2OH$	**(Iab)**
1	6-F	3-CH_3	$-CH_3$	**(Iac)**
1	5-F	3-CH_3	$-(CH_2)_4NH_2$	**(Iad)**
1	6-F	3-CH_3	$-(CH_2)_4NH_2$	**(Iae)**
1	5-F	3-CH_3	$-CH_3$	**(Iaf)**
1	5-F	3-CH_3	H	**(Iai)**

It will also be understood that many of the compounds in accordance with the invention may be in the form of pharmaceutically acceptable salts, especially acid addition salts derived from an acid selected for example from the group comprising: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzene-sulphonic, methanesulphonic and ethanesulphonic.

It should also be understood, however, that where reference is made in this specification to compounds of formula **(I)** such reference should be construed as extending not only to their pharmaceutically acceptable salts but also to other pharmaceutically acceptable bioprecursors (prodrug forms), especially amino acid amide derivatives as hereinbefore referred to, where relevant. Moreover, where any of the compounds referred to can exist in more than one enantiomeric form or contain atoms which have more than one

isotope, all such enantiomeric forms or isotopic compounds, mixtures thereof, and their preparation and uses are within the scope of the invention.

The invention also comprises the use of a 2-arylbenzazole compound as hereinbefore specified for making a medicament or pharmaceutical composition, especially for selective use in antitumor therapy.

As hereinafter more particularly described, pharmaceutical compositions or preparations in accordance with the invention for selective use in antitumor therapy will generally contain or provide a therapeutically effective antitumour amount of the active compound, and will be formulated in accordance with any of the methods well known in the art of pharmacy for administration in any convenient manner, and may for example be presented in unit dosage form admixed with at least one other ingredient providing a compatible pharmaceutically acceptable additive, carrier, diluent or pharmaceutically inert excipient.

Biological results

In vitro cytotoxicities

In carrying out the following cytotoxicity assays, the method used corresponds substantially to the following example:

Cells were maintained in a continuous logarithmic culture in RMPI 1640 with L-glutamine medium, supplemented with 10% fetal calf serum, penicillin (100 IU/ml) and streptomycin (100 µg/ml). The cells were mildly trypsinized for passage and for use in assays.

On day one, 180µl of trypsinized tumour cells (5×10^3 ml^{-1}) were placed in the wells of 96-well, flat-bottom microtiter plates. Columns 1 and 12 were filled with 300µl medium to protect from evaporation. The plates were incubated for 24 hours at 37°C and 5% CO_2 in air to allow the cells to adhere and resume exponential growth prior to the addition of

drugs. The compounds being tested were dissolved in DMSO and stored as 10mM stock solutions at 4°C, protected from light. Serial dilutions at a 10x concentration were prepared in growth medium so that the final concentration of DMSO exposed to cells did not exceed 1%.

On day two, 20µl of growth medium was added to the wells of column 2 to act as a control. 20µl of drug dilution was added to the other wells with the lowest concentration in column 3 and the highest concentration in column 11. The plates were incubated for 72 hours at 37°C and 5% CO_2 in air. Each compound was tested in triplicate. At the time of drug addition, a plate of untreated cells was read to provide an initial optical density value for use in the calculation of the IC_{50}.

On day five the plates were read. 50µl MTT (1mg/ml^{-1}) was added per well and the plates incubated for a further 4 hours. The MTT is metabolised to form a blue formazan product. The MTT solution was aspirated and 125µl DMSO:glycine buffer (4:1) was added. The plates were placed on a plate shaker until the formazan crystals had dissolved and absorbance was ready at 550nm on a plate reader.

For each compound tested, a dose response curve was obtained and the IC_{50} value (drug concentration at 50% inhibition of cell growth) was calculated.

It has surprisingly been found that many of the compounds of formula **(I)** are highly potent, inhibiting 50% cell growth at <10 nM. Examples of the results of *in vitro* cyctotoxicity tests carried out using MCF-7 and MDA-468 cell lines are presented at the end of this description in TABLE 1 which shows IC_{50} values as determined by 3-day MTT assays (n = 8) for a range of compounds in relation to MCF-7 and MDA 468 cell lines.

The selectivity of antitumor effect of the fluorinated compounds of the invention has been found to be very similar to that found for the prior art compounds disclosed in WO 96/26932, with antiproliferative activity observed in the same cell lines that were growth inhibited by their respective non-fluorinated parent compounds, e.g., breast MCF-7 and MDA 468 cells. Prostate PC 3 and non-malignant breast HBL 100 cells were unresponsive to compounds of the invention.

One feature of the prior art compounds is that they show a biphasic dose-response relationship specifically in sensitive cell lines: cell kill occurs at low nanomolar concentrations of the compounds, followed by a potentially undesirable proliferative response at low micromolar concentrations (termed the "second growth phase"). However, it has surprisingly been found that the biphasic response is eliminated in some compounds of the invention, especially when R^1 represents 5-F or 7-F as in compounds **Ik** and **Ih**.

In addition to breast (MCF-7, T-47D), ovarian (IGROV 1, OVCAR 3), and renal (TK 10) cell lines, the compounds of the invention wherein R^1 is for example 5-F have been found to be active against colon (HCC 2998) cell lines in a standard 2 day sulforhodamine B assay – in contrast, these colon cell lines respond to the non-fluorinated prior art compounds only after prolonged 6 day exposures.

Among the prodrugs, 2-(4'-amino-3'-methylphenyl)-5-fluoro-benzothiazole alanine (alanyl amide hydrochloride salt – compound **Iaf**) shows outstanding antitumour potency, with IC_{50} in MCF-7 cells > 5 fold lower than that of other amido prodrugs. None of these prodrugs elicits the biphasic dose-response.

NCI mean graphs of the amino acid salts are similar to those of their respective parent compound, with selective antitumour activity against certain ovarian (OVCAR-5), renal (TK-10) and breast (MCF-7, T-47D) cell lines.

In vivo xenograft studies

The compounds of formula **(Ib)** and **(Ik)** were evaluated for *in vivo* antitumor property in ER positive MCF-7 and ER negative MT-1 human breast tumor xenografts implanted in nude mice using the experimental details described at pages 11 and 12 of WO 96/26932. Significant growth inhibition of MCF-7 xenografts was observed with both compounds given i.p., with the 5-F compound of formula **(Ik)** being toxic at 12.5 mg/kg. In the MT-1 xenografts, the compound of formula **(Ik)** was toxic at 25 mg/kg; at the lower dose of 12.5 mg/kg, the (6-F) compound of formula **(Ib)** produced more pronounced growth inhibition than did the same dose of the compound of formula **(Ik)** although both analogues caused dose-dependent tumor growth inhibition and weight loss. Blood parameters (white blood cell and platelet counts) and the level of liver transaminases were not adversely affected by either compound.

The *in vitro* growth inhibitory property of the compounds of formula **(Iw)** and **(Iz)** is paralleled by significant *in vivo* growth retardation of human breast tumour xenografts (ER positive MCF-7 and ER negative MT-1) implanted in nude mice. At a dose of 12.5 mg/kg (given i.v.), the alanyl-prodrug of formula **(Iw)** caused a greater extent of growth retardation than its lysyl- counterpart of formula **(Iz)** against MCF-7 xenografts. Dose-dependent body weight loss was observed with the compound of formula **(Iz)**. In the MT-1 xenografts, the compound of formula **(Iw)** was toxic at 25 mg/kg, while the compound of formula **(Iz)** was toxic at both doses of 12.5 mg/kg and 25 mg/kg; moderate tumor growth inhibition was observed in surviving mice treated with either prodrug.

In the accompanying drawings there are illustrated typical results of tumour growth inhibition in tumour xenographs following drug treatment as detailed below.

Tumour growth inhibition observed with MCF7 xenografts treated with the compound 2-(4'-amino-3'-methylphenyl)benzothiazole (designated DF203) and compound **Ik** (conveniently designated 5F203) is shown in FIGURE 1 of the accompanying drawings. In FIGURE 2 of said drawings there is shown the tumour growth inhibition observed with COLO205 xenografts treated respectively with the alanyl prodrug form of DF203 (compound **Iv**), the 5F analogue of DF203 (compound **Ik**), and with the 6F analogue of DF203 (compound **Ib**).

Pharmacokinetic studies

Although amino acid amide prodrug compounds such as those of formulae **(Iw)**, **(Iz)** and **(Iad)** in the form of their hydrochloride salts have been found to be stable in rat and other mammalian plasma *in vitro*, it has surprisingly been found that these prodrugs are readily removed from such plasma and reconverted to their parent compound *in vivo*, e.g. when given to rats intravenously (i.v.) at a typical dose of 25 mg/kg, thereby demonstrating suitability for use as prodrugs.

By way of example, TABLE 2 below shows the plasma concentrations measured following administration to mice at a dose of 70μmol/kg of 5F203 (compound **Ik**) and the lysyl prodrug analogue thereof in the form of its dihydrochloride salt (compound **Iad**). A similar progressive increase in concentration of the parent compound 5F203 has also been observed following addition of said lysyl prodrug analogue of 5F203 (compound **Iad**) to a culture of MCF-7 cells.

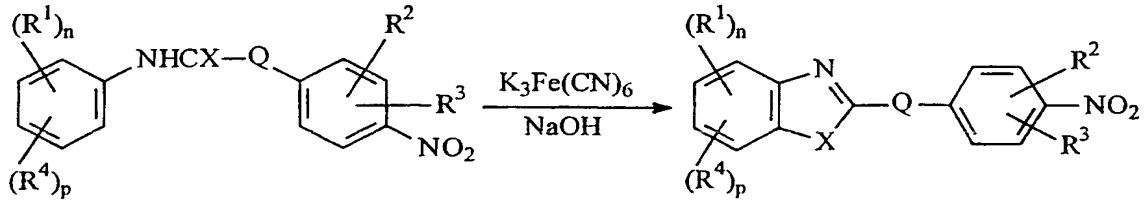
TABLE 2

Mean Sample Time (min)	Geometric Mean Plasma Concentration (μM) Compound **Iad**	Compound **Ik**
3.5	23.67	1.18
6.5	7.35	1.53
9.5	5.05	1.84
12.5	3.47	2.27
15.5	3.33	3.27
20.8	2.80	2.68
30.5	2.24	3.77
45.4	1.16	3.41
60.5	1.25	4.11
90.6	1.06	3.52
120.5	0.41	2.63
240.0	0.08	1.00
360.0	bld	0.59

Preparative Methods

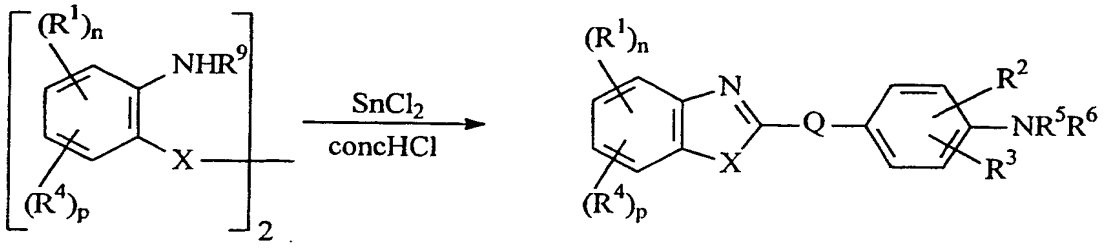
In most cases the compounds of formula **(I)** of the present invention can readily be synthesised by various routes from easily available starting materials. By way of example, several such general synthetic routes, designated Route A, Route B, Route C, Route D and Route E are described below. The substituents for the starting materials and products of these synthetic routes have the meanings given above in connection with the definition of the compound of general formula **(I)** unless otherwise stated.

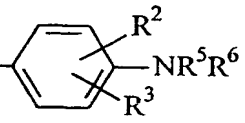
Route A



In the general method (Jacobsen cyclisation method) for Route A which is suitable when X = S, the starting material is the appropriate substituted thiobenzanilide which may be prepared by reacting an optionally substituted 4-nitrobenzoyl chloride with a solution of the appropriately substituted fluoroaniline and subsequently treating the oxybenzanilide product with Lawesson's reagent to form the thiobenzanilide. In a typical procedure, this thiobenzanilide (1 Mol. equiv.) is finely powdered and mixed with a little ethanol to form a wet paste. A 30% w/v solution of aqueous sodium hydroxide (8 Mol. equiv.) is added and diluted with water to form a suspension/solution of the thiobenzanilide in 10% w/v aqueous sodium hydroxide. Aliquots of this suspension/solution are then introduced dropwise at one minute intervals into a stirred solution of potassium ferricyanide (4 Mol. equiv.) in water at 80-90°C. The reaction mixture is heated for a further 30 minutes, then cooled. The product is collected, washed with water and crystallised. Further reduction, e.g. by heating under reflux with tin(II) chloride dihydrate in ethanol solvent, yields a compound of formula **(I)** wherein R^5 and R^6 each represent hydrogen. Methods well known in the art may be used to prepare further compounds of formula **(I)** where R^5 and/or R^6 do not represent hydrogen.

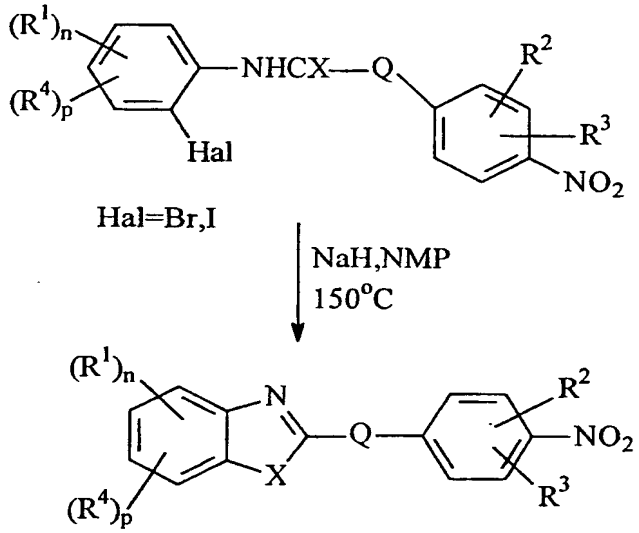
Route B



wherein R^9 is —CO—Q— 

In the so-called Disulphide general method of Route B which is also suitable when X = S, typically the disulphide starting material is added together with tin(II) chloride to a solution of conc HCl, ethanol and water. The reaction mixture is heated under reflux for 15 hours, cooled to 25°C and poured into water. Sodium hydroxide is added slowly, and the mixture stirred for 60 minutes. The precipitate is filtered from solution, and washed with water to leave a solid which is purified by column chromatography (dichloromethane) followed by recrystallisation from ethanol to give clear needles. A particular example of the use of this Disulphide Route including preparation of the disulphide starting material is hereinafter more fully described in relation to EXAMPLE 11.

Route C

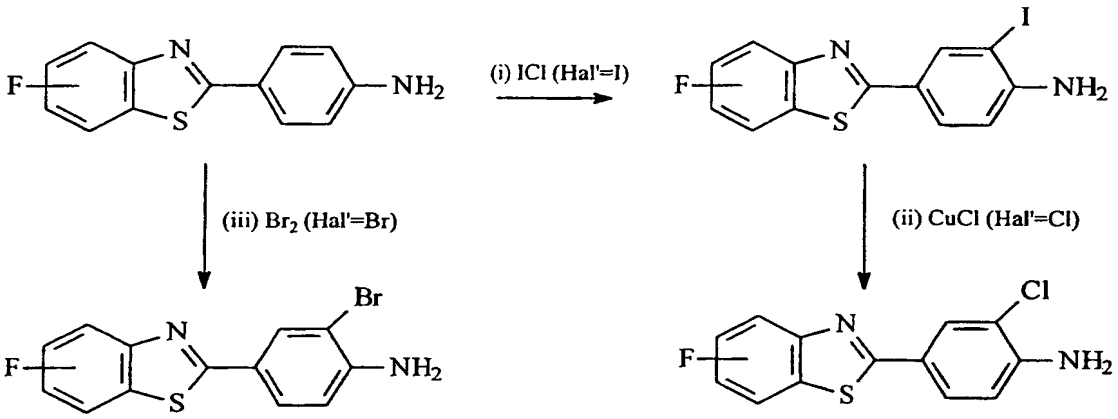


In the general method for Route C, sodium hydride (1.1 mol. equiv) is slowly added to a solution of starting material (1.0 mol. equiv) in N-methyl-2-pyrrolidinone (NMP) at room temperature with stirring. The mixture is heated at 150°C for one hour then allowed to cool. Water (50ml) is then added and the precipitate collected by filtration and dried *in vacuo* to give the solid product.

Reduction, e.g. by refluxing with tin(II) chloride in ethanol, yields a compound of formula **(I)** wherein R^5 and R^6 each represent hydrogen. Methods well known in the art may be used to prepare further compounds of formula **(I)** where R^5 and/or R^6 do not represent hydrogen.

This method is generally applicable but is especially useful for the synthesis of compounds with 7-fluoro, 5-fluoro, 5,6-difluoro and 6,7-difluoro substituents.

Route D



Route D is for 3'-halogenation of compounds of formula **(I)**. The general methods for each variant are as follows:

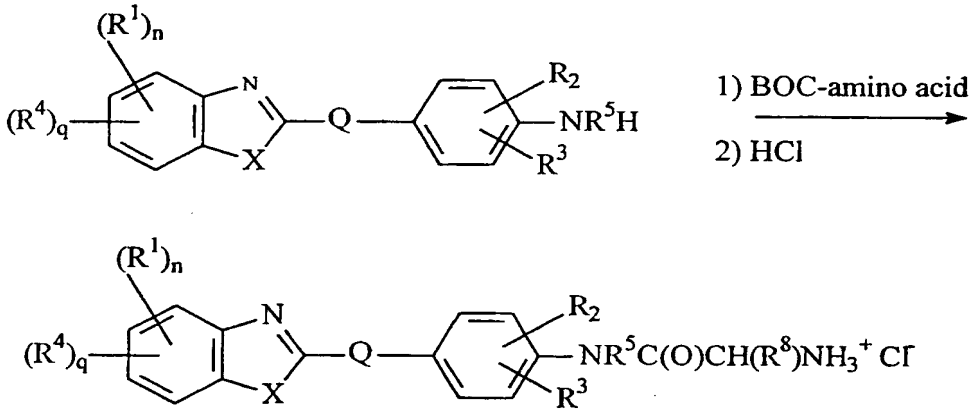
(i) in the general method for iodination, iodine monochloride ICl is added to a solution of the starting material in acetic acid at 25°C. The resulting solution is stirred for 2 hours, then the solvent is removed under vacuum. The residue is dissolved in chloroform and washed with aqueous sodium carbonate, aqueous sodium thiosulfate and water. Evaporation of the solvent, is followed by column chromatography (chloroform) and recrystallisation from methanol giving needles.

(ii) in the general method for chlorination, a solution of the 3'-iodo compound prepared as in (i) above and copper(I) chloride in DMF is

heated under reflux overnight. After cooling, the reaction mixture is poured into ethyl acetate, the precipitated solids are filtered off and the resulting solution evaporated to dryness. The product is purified by column chromatography (dichloromethane) followed by recrystallization from methanol to give a pale green solid.

(iii) in the general method for bromination, bromine is added to a solution of the original starting material in dichloromethane at 10°C. The resulting solution is stirred for 10 min, then poured into water/ice. The organic layer is removed and washed with 10% sodium thiosulfate, water and evaporated. The product is purified by column chromatography (dichloromethane) to leave a white solid.

Route E



Route E is for preparing amino acid prodrug derivatives.

A compound of formula **(I)** wherein R^6 represents hydrogen (7.75mmol) is dissolved in dichloromethane (100ml) and stirred at room temperature. To this solution is added 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (2.3mmol), HOBt (2.3mmol) and the appropriate BOC protected amino acid (2.3mmol). This procedure is repeated and the reaction is continued until a clear solution is obtained. The solvent is removed under vacuum and the

resulting oil purified by column chromatography (2% methanol/dichloromethane). Recrystallisation from ethanol gives a white solid.

The BOC protected amino acid derivative thus obtained (3.5mmol) is dissolved in dichloromethane (20ml). Dry HCl gas is bubbled through the solution to saturate it, then the reaction mixture is stirred for a further 2 hrs at 25°C. The precipitate is filtered from solution and washed with dichloromethane (10ml), to leave a bright yellow crystalline solid. Recrystallisation, if required, is carried out using methanol/acetone.

Therapeutic Use

As already indicated, compounds of this invention have been found to inhibit tumor cell proliferation and to have significant selective antitumor activity. Antitumor activity may be evidenced by reduction of tumor cell number in mammals bearing cancer tumors, e.g. breast cancer tumors, and a consequent increase in survival time as compared to a control provided by animals which are untreated. Antitumor activity is further evidenced by measurable reduction in the size of solid tumors following treatment with the compounds of this invention compared to the tumors of untreated control animals.

Accordingly, as previously stated the compounds of the present invention are of particular interest for the treatment of a range of selected cancer tumors, and the invention further provides a method for the treatment of a patient suffering from certain kinds of cancer. For this purpose, a therapeutically effective non-toxic amount of a compound of formula **(I)** as hereinbefore defined, may be suitably administered, orally, parenterally (including subcutaneously, intramuscularly and intravenously), or topically. The administration will generally be carried out repetitively at intervals, for example once or several times a day.

The amount of the compound of formula (I) which is required in order to be effective as an antitumor agent for treating mammals will of course vary and is ultimately at the discretion of the medical or veterinary practitioner treating the mammal in each particular case. The factors to be considered by such a practitioner, e.g. a physician, include the route of administration and pharmaceutical formulation; the mammal's body weight, surface area, age and general condition; and the chemical form of the compound to be administered. However, a suitable effective antitumor dose may be in the range of about 1.0 to about 75 mg/kg bodyweight, preferably in the range of about 5 to 40mg/kg with most suitable doses being for example in the range of 10 to 30mg/kg. In daily treatment for example, the total daily dose may be given as a single dose, multiple doses, e.g. two to six times per day, or by intravenous infusion for any selected duration. For example, in the case of a 75kg mammal, the dose range could be about 75 to 500mg per day, and it is expected that a typical dose would commonly be about 100mg per day. If discrete multiple doses are indicated, treatment might typically be 50mg of the compound of formula (I), given 4 times per day in the form of a tablet, capsule, liquid (e.g. syrup) or injection.

While it may be possible for the compounds of formula (I) to be administered alone as the raw chemical, it is preferable to present the compounds as a pharmaceutical formulation. Formulations of the present invention, for medical use, will generally comprise the compound of formula (I) together with one or more pharmaceutically acceptable carriers and, optionally, any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention therefore further provides a pharmaceutical formulation comprising a compound of formula **(I)** together with a pharmaceutically acceptable carrier thereof.

The possible formulations include those suitable for oral, rectal, topical and parenteral (including subcutaneous, intramuscular and intravenous) administration or for administration to the lung or another absorptive site such as the nasal passages.

All methods of formulation will generally include the step of bringing the compound of formula **(I)** into association with a carrier which constitutes one or more accessory ingredients. Usually, the formulations are prepared by uniformly and intimately bringing the compound of formula **(I)** into association with a liquid carrier or with a finely divided solid carrier or with both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the compound of formula **(I)**; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught. The compound of formula **(I)** may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of formula **(I)** in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered compound of formula **(I)** with any suitable carrier.

A syrup may be made by adding the compound of formula (I) to a concentrated, aqueous solution of a sugar, for example sucrose, to which may be added any desired accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter.

Formulations suitable for parental administration conveniently comprise a sterile aqueous preparation of the compound of formula (I) which is preferably isotonic with the blood of the recipient. An injectable formulation may be made up for example with the compound 2-(4'-amino-3'-methylphenyl)-5-fluorobenzothiazole in the form of a water-soluble lysyl amide dihydrochloride salt dissolved in saline with Tween 80™ (0.05%) or 5% dextrose in water. A typical dose range in this case for use in treating humans would be 1-100mg/m^2.

In addition to the aforementioned ingredients, formulations of this invention, for example ointments, creams and the like, may include one or more accessory ingredients, for example a diluent, buffer, flavouring agent, binder, surface active agent, thickener, lubricant and/or a preservative (including an antioxidant) or other pharmaceutically inert excipient.

The compounds of this invention may also be made up for administration in liposomal formulations which can be prepared by methods well-known in the art.

Thus, as already indicated, the invention also comprises use of a compound of formula (I) as herein defined for the manufacture of a medical preparation, especially for use in the treatment of cancer.

EXAMPLES

The preparation of a number of particular compounds which are considered to be of especial interest for use as active therapeutic substances to inhibit proliferation of at least certain cancer cells and which provide examples of preferred embodiments of the invention (or examples of reference compounds for comparison purposes) will now be described in more detail, together with some general procedures for specific types of reactions. Some of the compounds described can also be useful as intermediates for the preparation of compounds of other embodiments. The compound or formula reference codes used elsewhere in this description are also quoted where applicable. It should be understood, however, that these specific examples are not intended to be construed in any way as limiting the scope of the invention.

EXAMPLE 1

4-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ia)**

3-Methyl-4-nitrobenzoyl chloride (0.2 mol) was added slowly to a solution of 2-fluoroaniline (0.2 mol) in pyridine (100 ml). The resulting solution was heated under reflux for 60 min, then poured into water (300 ml). The precipitate was filtered from solution, washed with water (100 ml), followed by methanol to afford a white solid.

Lawesson's reagent (0.07 mol) was added to a solution of the benzanilide obtained (0.1 mol) in HMPA (50 ml). The resulting solution was heated at 100°C for 15 hr, then poured into water (300 ml). The product was extracted into diethyl ether (3 x 300 ml) and washed with water (3 x 200 ml). Evaporation of the solvent followed by recrystallization from methanol gave a bright orange solid.

A solution of the fluoro substituted thiobenzanilide thus obtained (0.2 mol) in aqueous sodium hydroxide (1.8 mol in 50 ml water) containing ethanol (5 ml)

was added dropwise to a solution of potassium ferricyanide (0.8 mol) in water (20 ml) at 90°C over a period of 60 min. The resulting solution was stirred at 90°C for a further 2 hr, then cooled in ice. The precipitate was filtered from solution and washed with water (100 ml). The product was purified by column chromatography (30% hexane/chloroform) to leave a bright yellow solid.

The product of the previous step (0.03 mol) and tin(II) chloride dihydrate (0.15 mol) were suspended in ethanol (150 ml) and heated under reflux for 2 hrs. The solvent was removed under vacuum and the resulting oil taken up in ethyl acetate (700 ml). The organic layer was washed with 2 M sodium hydroxide (2 x 200 ml), water (100 ml) and salt brine (30 ml). Removal of the solvent under vacuum followed by recrystallization from methanol gave the title compound as a pale yellow solid.

mp 203-205°C; IR 3491, 3369 (NH_2), 1624 (C=N) cm^{-1}; ^1H NMR (DMSO-d6) δ 7.86 (1H, dd, *J* 1.5, 8.5Hz, H-7), 7.71 (1H, d, *J* 2Hz, H-2'), 7.66 (1H, dd, *J* 2, 8.25Hz, H-6'), 7.37-7.30 (2H, m, H-5, H-6), 6.73 (1H, d, *J* 8.25, H-5'), 5.78 (2H, brs, NH_2), 2.17 (3H, s, CH_3); MS (CI) *m/z* 259.5 (M+1); Anal ($C_{14}H_{11}N_2SF$) C, H, N.

EXAMPLE 2

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ib)**

The method of Example 1 was carried out using 4-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 203-205°C; IR 3467, 3306 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 3

4-Fluoro-2-(4'-aminophenyl)benzothiazole **(Ic)**

The method of Example 1 was carried out using 4-nitrobenzoyl chloride instead of 3-methyl-4-nitrobenzoyl chloride. The title compound was obtained as a pale yellow solid.

mp 219-221°C; IR 3456, 3350 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 4

6-Fluoro-2-(4'-aminophenyl)benzothiazole **(Id)**

The method of Example 1 was carried out using 4-nitrobenzoyl chloride instead of 3-methyl-4-nitrobenzoyl chloride and 4-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 152-155°C; IR 3333, 3219 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 5

4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ie)**

The method of Example 1 was carried out 2,3-difluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 204-205°C; IR 3466, 3387 (NH_2), 1616 (C=N) cm^{-1}.

EXAMPLE 6

4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(If)**

The method of Example 1 was carried out using 2,4-difluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 197-199°C; IR 3475, 3385 (NH_2), 1622 (C=N) cm^{-1}.

EXAMPLE 7

5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ig)**

The method of Example 1 was carried out using 3,5-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 201-203°C; IR 3483, 3323 (NH_2), 1616 (C=N) cm^{-1}.

EXAMPLE 8

7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole (**Ih**)

This Example made use of the general preparative method designated Route C. 3-Methyl-4-nitrobenzoyl chloride (0.2 mol) was added slowly to a solution of 2-bromo-3-fluoroaniline (0.2 mol) in pyridine (100 ml). The resulting solution was heated under reflux for 60 min, then poured into water (300 ml). The precipitate was filtered from solution, washed with water (100 ml), followed by methanol to afford a white solid.

Lawesson's reagent (0.07 mol) was added to a solution of the benzanilide obtained (0.1 mol) in HMPA (50 ml). The resulting solution was heated at 100°C for 15 hr, then poured into water (300 ml). The product was extracted into diethyl ether (3 x 300 ml) and washed with water (3 x 200 ml). Evaporation of the solvent followed by recrystallization from methanol gave a bright orange solid.

Sodium hydride (0.22 mol) was slowly added to a solution of the fluoro substituted thiobenzanilide thus obtained (0.2 mol) in N-methyl-2-pyrrolidinone (2 mol) at room temperature with stirring. The mixture was heated at 150°C for one hour then allowed to cool. Water (50ml) was then added and the precipitate collected by filtration and dried *in vacuo* to give the product as a white solid.

The product of the previous step (0.03 mol) and tin(II) chloride dihydrate (0.15 mol) were suspended in ethanol (150 ml) and heated under reflux for 2 hours. The solvent was removed under vacuum and the resulting oil taken up in ethyl acetate (700 ml). The organic layer was washed with 2 M sodium hydroxide (2 x 200 ml), water (100 ml) and salt brine (30 ml). Removal of the solvent under vacuum followed by recrystallization from methanol gave the title compound as a pale yellow solid.

mp 175-177°C; IR 3021, 1621 (C=N), 1470, 1215, 750 cm^{-1}.

EXAMPLE 9

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ii)**

The method of Example 8 was carried out using 2-bromo-4,5-difluoroaniline instead of 2-bromo-3-fluoroaniline. The product was obtained as a pale yellow solid.

mp 226-228°C; IR 3497, 3333, 1632, 1466, 1454, 1406, 1314, 1142 cm^{-1}.

EXAMPLE 10

6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ij)**

The method of Example 8 is carried out using 2-bromo-5,6-difluoroaniline instead of 2-bromo-3-fluoroaniline.

EXAMPLE 11

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ik)**

"Disulphide Route"

2-Amino-5-fluorobenzothiazole (5 g, 0.03 mol) was added to a solution of potassium hydroxide (25 g) in water (50 ml). The resulting mixture was heated under reflux for 5 hr, after which complete solution had occurred. After cooling, the reaction mixture was made acidic (pH 6) by the addition of acetic acid. A further portion of water (50 ml) was added and the resulting mixture stirred overnight. The solid precipitate was filtered from solution and recrystallized from ethanol/water to give bis-(2-amino-5-fluorophenyl) disulphide as a pale yellow solid.

3-Methyl-4-nitrobenzoyl chloride (1.45 g, 7.3 mmol) was added to a solution of bis-(2-amino-5-fluorophenyl) disulfide (1 g, 3.65 mmol) in pyridine (10 ml). The resulting mixture was heated under reflux for 30 min, then poured into water (50 ml). The precipitate was filtered from solution, and washed with water

(50 ml) to leave bis-[2-(3'-methyl-4'-nitrobenzanilide)-5-fluorophenyl] disulfide as a pale yellow solid.

Then, as described in relation to the preparative method designated Route B, to a solution of conc HCl (10 ml), ethanol (20 ml) and water (2 ml) was added the bis-[2-(3'-methyl-4'-nitrobenzanilide)-5-fluorophenyl] disulfide (1 g, 1.6 mmol) together with tin(II) chloride (1.86 g, 9.8 mmol). The reaction mixture was heated under reflux for 15 hr, cooled to 25°C and poured into water (75 ml). Sodium hydroxide (2 g) was added slowly, and the mixture stirred for 60 min. The precipitate was filtered from solution, and washed with water (10 ml) to leave a yellow solid which was purified by column chromatography (dichloromethane) followed by recrystallization from ethanol to give colorless needles.

mp 195-196°C; IR 3433, 3302 (NH_2), 1622 (C=N) cm^{-1}.

EXAMPLE 12

5-Fluoro-2-(4'-aminophenyl)benzothiazole **(II)**

4-Nitrobenzoyl chloride (1.35 g, 7.3 mmol) was added to a solution of bis-(2-amino-5-fluorophenyl) disulfide prepared as described in Example 11 (1 g, 3.65 mmol) in pyridine (10 ml). The resulting mixture was heated under reflux for 30 min, then poured into water (50 ml). The precipitate was filtered from solution, and washed with water (50 ml) to leave bis-[2-(4'-nitrobenzanilide)-5-fluorophenyl] disulfide as a pale yellow solid.

To a solution of conc HCl (10 ml), ethanol (10 ml) and water (2 ml) was added bis-[2-(4'-nitrobenzanilide)-5-fluorophenyl] disulfide (1 g, 1.7 mmol) and tin(II) chloride (1 g, 5.2 mmol). The reaction mixture was heated under reflux for 15 hr, cooled to 25°C and poured into water (75 ml). Sodium hydroxide (2 g) was added slowly, and the mixture stirred for 60 min. The precipitate was filtered from solution, and washed with water (10 ml) to leave a yellow solid which was

purified by column chromatography (dichloromethane) followed by recrystallization from ethanol to give colorless needles.

mp 153-155°C; IR 3460, 3290 (NH_2), 1637 (C=N) cm^{-1}.

EXAMPLE 13

4-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole **(Im)**

A solution of the 4-fluoro-2-(4'-aminophenyl)benzothiazole prepared as described in Example 3 (4.5 mmol) in acetic acid (20 ml) was added dropwise to a solution of iodine monochloride (5.8 mmol) in acetic acid (20 ml) at 25°C. The resulting solution was stirred for 2 hr, then the solvent was removed under vacuum. The residue was dissolved in chloroform (100 ml) and washed with aqueous sodium carbonate (50 ml), aqueous sodium thiosulfate (50 ml) and water (50 ml). Evaporation of the solvent, followed by column chromatography (chloroform) and recrystallization from methanol gave pale cream needles.

mp 210-211°C; IR 3474, 3377 (NH_2), 1610 (C=N) cm^{-1}.

EXAMPLE 14

5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole **(In)**

The method of Example 13 was carried out using the 5-fluoro-2-(4'-aminophenyl)benzothiazole prepared as described in Example 12 instead of 4-fluoro-2-(4'-aminophenyl) benzothiazole.

mp 187-188°C; IR 3447, 3317 (NH_2), 1612 (C=N) cm^{-1}.

EXAMPLE 15

6-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole **(Io)**

The method of Example 13 was carried out using the 6-fluoro-2-(4'-aminophenyl)benzothiazole prepared as described in Example 4 instead of 4-fluoro-2-(4'-aminophenyl) benzothiazole.

mp 198-200°C; IR 3445, 3290 (NH_2), 1620 (C=N) cm^{-1}.

EXAMPLE 16

4-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole **(Ip)**

A solution of the 4-fluoro substituted 2-(4'-amino-3'-iodophenyl)benzothiazole prepared as described in Example 13 (1.35 mmol) and copper(I) chloride (6.75 mol) in DMF (5 ml) was heated under reflux overnight. After cooling, the reaction mixture was poured into ethyl acetate (100 ml), the precipitated solids were filtered off and the resulting solution evaporated to dryness. The product was purified by column chromatography (dichloromethane) followed by recrystallization from methanol to give a pale green solid.

mp 181-183°C; IR 3477, 3381 (NH_2), 1620 (C=N) cm^{-1}.

EXAMPLE 17

5-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole **(Iq)**

The method of Example 16 was carried out using the 5-fluoro substituted 2-(4'-amino-3'-iodophenyl)benzothiazole prepared as described in Example 14 instead of 4-fluoro substituted 2-(4'-amino-3'-iodophenyl)benzothiazole.

mp 177-178°C; IR 3481, 3369 (NH_2), 1631 (C=N) cm^{-1}.

EXAMPLE 18

6-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole **(Ir)**

The method of Example 16 was carried out using the 6-fluoro substituted 2-(4'-amino-3'-iodophenyl)benzothiazole prepared as described in Example 15 instead of 4-fluoro substituted 2-(4'-amino-3'-iodophenyl)benzothiazole.

mp 194-195°C; IR 3472, 3310 (NH_2), 1628 (C=N) cm^{-1}.

EXAMPLE 19

4-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole **(Is)**

Bromine (0.8 mmol) was added to a solution of the 4-fluoro-2-(4'-aminophenyl) benzothiazole prepared as described in Example 3 (0.8 mmol) in dichloromethane (20 ml) at 10°C. The resulting solution was stirred for 10 min, then poured into water/ice (10 ml). The organic layer was removed and washed with 10% sodium thiosulfate (10 ml), water (10 ml) and evaporated. The product was purified by column chromatography (dichloromethane) to leave a white solid.

mp 211-213°C; IR 3416, 3379 (NH_2), 1618 (C=N) cm^{-1}.

EXAMPLE 20

5-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole **(It)**

The method of Example 19 was carried out using the 5-fluoro-2-(4'-aminophenyl) benzothiazole prepared as described in Example 12 instead of 4-fluoro-2-(4'-aminophenyl) benzothiazole.

mp 181-183°C; IR 3464, 3311 (NH_2), 1612 (C=N) cm^{-1}.

EXAMPLE 21

6-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole **(Iu)**

The method of Example 19 was carried out using the 6-fluoro-2-(4'-aminophenyl) benzothiazole prepared as described in Example 4 instead of 4-fluoro-2-(4'-aminophenyl) benzothiazole.

mp 209-211°C; IR 3462, 3300 (NH_2), 1626 (C=N) cm^{-1}.

EXAMPLE 22

2-(4'-Aminophenyl)benzothiazole alanyl amide hydrochloride salt **(Iv)**

2-(4'-Aminophenyl)benzothiazole (7.75mmol) was dissolved in dichloromethane (100ml) and stirred at room temperature. To this solution was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (2.3mmol), HOBt (2.3mmol) and Boc protected alanine (2.3mmol). After

stirring for 24 hrs a further 2.3mmol of each reactant was added, and stirring continued for a further 24 hrs. This procedure was repeated twice more and stirring continued for a further 3 days, until a clear solution formed. The solvent was removed under vacuum and the resulting oil purified by column chromatography (2% methanol/dichloromethane). Recrystallisation from ethanol gave a white solid.

The Boc protected amino acid derivative thus obtained (3.5mmol) was dissolved in dichloromethane (20ml). Dry HCl gas was bubbled through the solution to saturate it, then the reaction mixture was stirred for a further 2 hrs at 25°C. The precipitate was filtered from solution and washed with dichloromethane (10ml), to leave a bright yellow crystalline solid.

mp 258-259°C; MS (AP) *m/z* 298 (M+1).

EXAMPLE 23

2-(4'-Amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt **(Iw)**

The title compound was prepared using the method of Example 22 but with 2-(4'-amino-3'-methylphenyl)benzothiazole instead of 2-(4'-aminophenyl)-benzothiazole.

mp 272-274°C; MS (AP) *m/z* 312 (M+1).

EXAMPLE 24

2-(4'-Amino-3'-chlorophenyl)benzothiazole alanyl amide hydrochloride salt **(Ix)**

The title compound was prepared using the method of Example 22 but with 2-(4'-amino-3'-chlorophenyl)benzothiazole instead of 2-(4'-aminophenyl)-benzothiazole.

mp 240-243°C; MS (AP) *m/z* 332 (M+1).

EXAMPLE 25

2-(4'-Aminophenyl)benzothiazole lysine amide dihydrochloride salt **(Iy)**

The title compound was prepared using the method of Example 22 but with BOC protected lysine instead of BOC protected alanine.

mp 296-298°C; MS (AP) *m/z* 355 (M+1).

EXAMPLE 26

2-(4'-Amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt **(Iz)**

The title compound was prepared using the method of Example 22 but with 2-(4'-amino-3'-methylphenyl)benzothiazole instead of 2-(4'-amino-phenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 290-293°C; MS (AP) *m/z* 369 (M+1).

EXAMPLE 27

2-(4'-Amino-3'-chlorophenyl)benzothiazole lysyl amide dihydrochloride salt **(Iaa)**

The title compound was prepared using the method of Example 22 but with 2-(4'-amino-3'-chlorophenyl)benzothiazole instead of 2-(4'-aminophenyl)-benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 278-279°C; MS (AP) *m/z* 389 (M+1).

EXAMPLE 28

2-(4'-Amino-3'-methylphenyl)benzothiazole seryl amide hydrochloride salt **(Iab)**

The title compound was prepared using the method of Example 22 but with 2-(4'-amino-3'-methylphenyl)benzothiazole instead of 2-(4'-aminophenyl) benzothiazole and BOC protected serine instead of BOC protected alanine.

mp 265-269 °C; MS (CI) *m/z* 328 (M+1).

EXAMPLE 29

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt **(Iac)**

The title compound was prepared using the method of Example 22 but with 6-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 2 instead of 2-(4'-aminophenyl) benzothiazole.

mp 282-285°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 30

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt **(Iad)**

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 290-294°C; MS (CI) *m/z* 387.4 (M+1).

EXAMPLE 31

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt **(Iae)**

The title compound was prepared using the method of Example 22 but with 6-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 2 instead of 2-(4'-aminophenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 298-303°C; MS (CI) *m/z* 387.2 (M+1).

EXAMPLE 32

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt **(Iaf)**

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole.

mp 280-284°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 33

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt salt **(Iai)**

The title compound is prepared using the method of Example 22 but with 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4'-aminophenyl)benzothiazole and with BOC protected glycine instead of BOC protected alanine.

EXAMPLE 34

5-Bromo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iaj)**

Synthesis is analogous to that of 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ik)** as described in Example 11 but starting with 5-bromo-2-(4'-amino-3'-methylphenyl)benzothiazole.

Yield = 75%; mp 224-227°C; IR 3465, 3342 cm^{-1}; MS (CI) *m/z* 318.9, 320.6 (M+1).

EXAMPLE 35

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iak)**

This was synthesised via a Jacobson cyclisation reaction from the appropriate benzanilide following the method of Route A and was separated from the 7-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 92%; mp 200-202°C; IR 3429, 3288 cm^{-1}; MS (CI) *m/z* 367.1 (M+1).

This compound can also be prepared from the appropriate 3-iodoaniline using the "Disulphide Route" previously referred to.

EXAMPLE 36

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole **(Ial)**

This was synthesised via Jacobson cyclisation, as above. It was separated from the 5-iodo isomer by column chromatography (25% hexane / dichloromethane) prior to reduction of the nitro group to amine.

Yield = 93%; mp 158-159°C; IR 3477, 3306 cm^{-1}; MS (CI) *m/z* 366.9 (M+1).

EXAMPLE 37

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole **(Iam)**

Acetyl Chloride (0.09g, 1.55mmol) was added to a solution of 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole (0.2g, 0.78mmol) in chloroform (5ml) containing triethylamine (86mg, 0.85mmol). The resulting solution was stirred for 30min, then poured into water (20ml). The organic layer was removed, dried (Na_2SO_4) and evaporated. Recrystallisation from ethanol gave a white solid.

Yield = 86%; mp 219-221°C; MS (CI) *m/z* 301.3 (M+1).

EXAMPLE 38

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Ian)**

5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole (5g, 0.0135mol), copper cyanide (3.65g, 0.04mol) and DMF (100ml) were heated under reflux for 6 hrs, cooled and the solvent removed under vacuum. The residue was stirred in water (50ml) for 30mins, then the product extracted with ethyl acetate (2 x 100ml). The combined extracts were dried (Na_2SO_4), evaporated and the residue recrystallised from ethanol to give a white solid.

Yield = 88%; mp 268-270°C; IR 3464, 3369, 2218 (CN) cm^{-1}; MS (CI) *m/z* 270.1 (M+1).

EXAMPLE 39

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Iao)**

This was synthesised from 4-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 18%; mp 225-227°C; IR 3471, 3366, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 40

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole **(Iap)**

This was synthesised from 6-fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole by a method analogous to that used for 5-fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole.

Yield = 12%; mp 258-260°C; IR 3412, 2216 (CN), 1642 cm^{-1}; MS (CI) *m/z* 270 (M+1).

EXAMPLE 41

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole **(Iaq)**

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole (1g, 3.75mmol) was dissolved in 80% sulfuric acid (50ml) and heated at 100°C for 2 hrs. After cooling, the reaction mixture was diluted with water (100ml) and the pH adjusted to 7.5 using 50% sodium hydroxide. The product was extracted with ethyl acetate (3 x 50ml), the extracts dried (Na_2SO_4) and evaporated to leave a yellow solid which was taken up in THF (20ml) and added dropwise to a solution of $LiAlH_4$ (0.7g, 0.019mol) in THF (15ml). After stirring at 25°C for 2 hrs, water (20ml) was added and the product extracted with ethyl acetate (3 x

50ml). The organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (10% ethyl acetate /dichloromethane) to leave a yellow powder.

Yield = 34%; mp 242-245°C; IR 3379, 3333, 1448cm^{-1}; MS (CI) *m/z* 275.1 (M+1).

EXAMPLE 42

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt **(Iar)**

Synthesised by same method as 5-fluoro analogue **(Iaf)**.

Yield = 96%; mp 268-270°C; MS (CI) *m/z* 348.0 (M+1).

EXAMPLE 43

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride **(Ias)**

Synthesised by same method as 5-fluoro analogue **(Iad)**.

Yield = 74%; mp 278-281°C; MS (CI) *m/z* 405.0 (M+1).

EXAMPLE 44

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole **(Iat)**

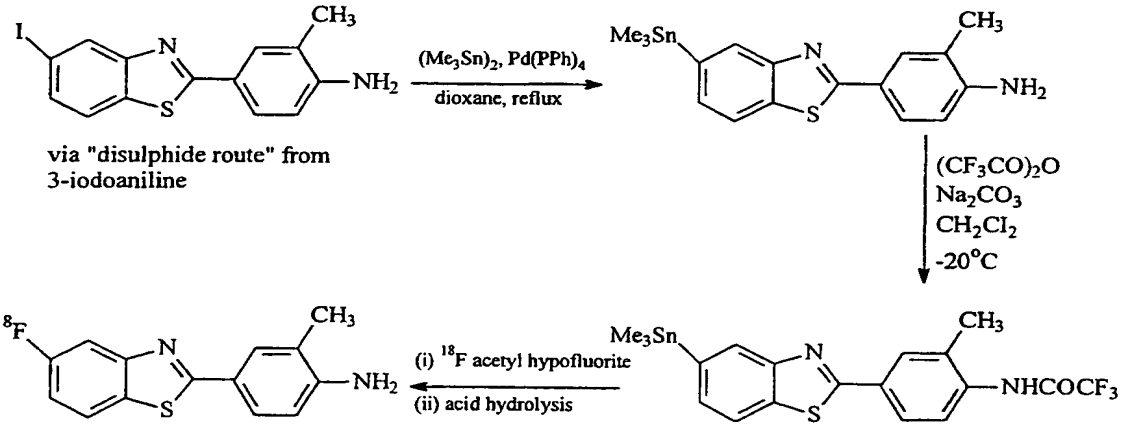
5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole (Compound **Iak**) (1.4g, 4.12mmol) and tetrakis triphenylphosphine palladium (48mg, 0.41mmol) were dissolved in dioxane (20ml) and placed under nitrogen. Hexamethylditin (5g, 0.15mol) was added and the resulting solution heated under reflux for 4hrs. The precipitated palladium was filtered from solution and washed with ethyl acetate (50ml). The organic fractions were evaporated and chromatographed (chloroform) to leave a white waxy solid. Recrystallisation from ethanol gave clear needles.

Yield = 85%; mp 158-160°C; MS (CI) *m/z* 402.8, 403.4, 404.9, 405.5 (M+1).

EXAMPLE 45

5-^{18}Fluoro-2-(4'-amino-3'-methylbenzothiazole)

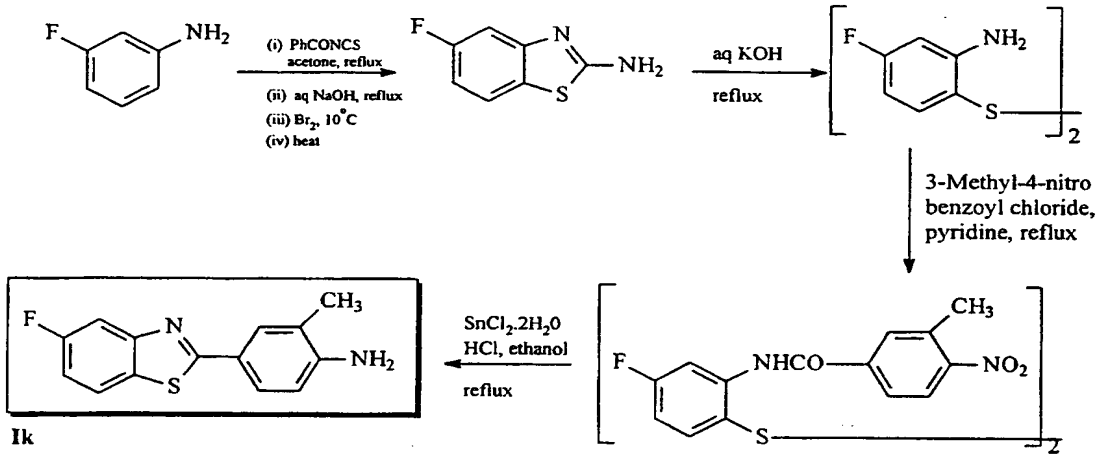
The compound **Iat** of Example 44 can be used as an intermediate in the preparation of the above ^{18}F labelled 5-fluoro compound from the corresponding 5-iodo substituted compound mentioned earlier. In this case the compound **Iat** is reacted at -20°C with $(CF_3CO)_2O$ in the presence of Na_2CO_3 and CH_2Cl_2 to form the trifluoroacetyl derivative which is then converted into the title compound by reacting with ^{18}F acetyl hypofluorite followed by acid hydrolysis. The overall scheme is depicted in the diagram below.



Of the compounds described above, the compound 5-fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole **Ik** and its lysyl amino acid amide prodrug **Iad**, in the form for instance of its water soluble dihydrochloride salt prepared as in Example 30 from its parent compound, are of especial interest for clinical use as effective antitumour agents. The solubility of this particular prodrug **Iad** in water and its chemical robustness makes it very suitable for parenteral administration as an injectable formulation, sterilised by filtration, after which it becomes converted *in vivo* to the 5-fluoro substituted compound **Ik**.

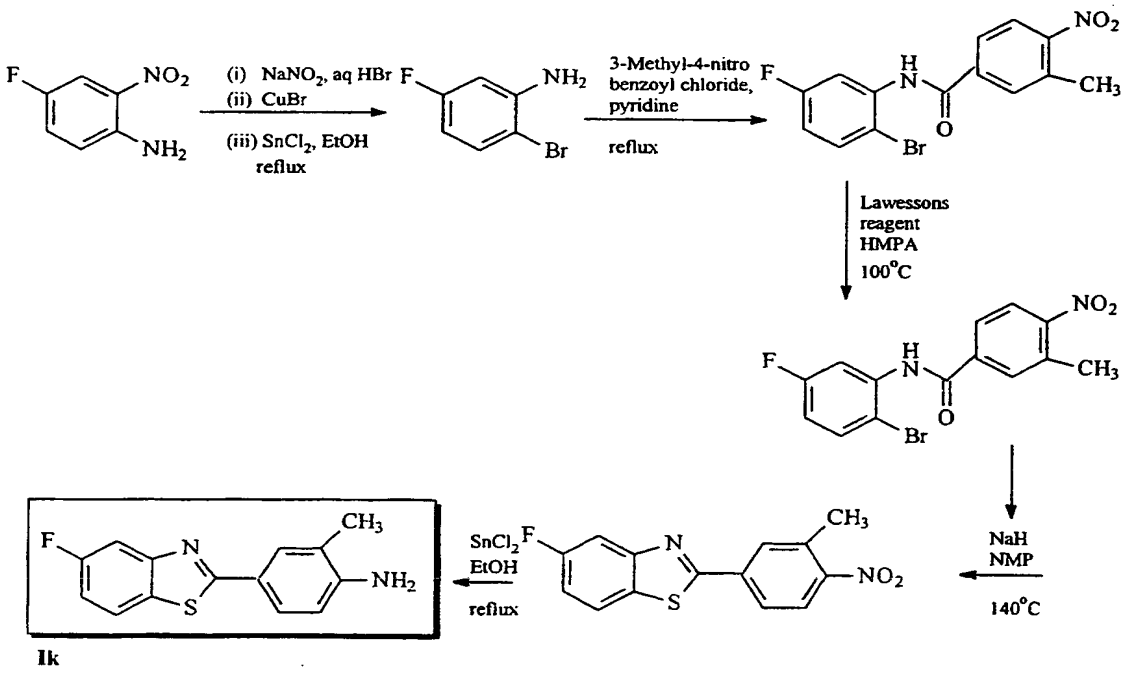
As an alternative to the "disulphide" preparative method described for compound **Ik** in Example 11, it may also be prepared by a "Regiospecific Cyclisation" Route involving in part the general method of Route C. Both these schemes are illustrated in the diagram below, together with the scheme for converting the compound **Ik** into the prodrug **Iad**.

"Disulphide" Route



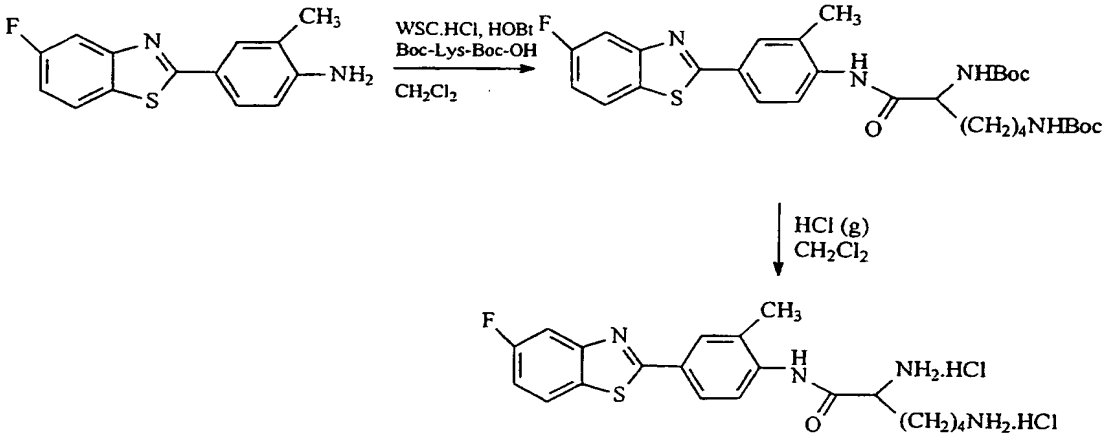
Ik

"Regiospecific Cyclisation" Route



Ik

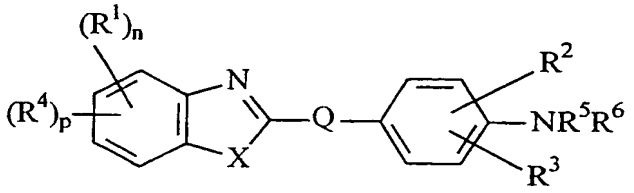
Conversion of Compound **Ik** into prodrug **Iad**



As will be seen, the invention presents a number of different aspects and it should be understood that it embraces within its scope all novel and inventive features and aspects herein disclosed, either explicitly or implicitly and either singly or in combination with one another. This includes the methods or processes for preparing or synthesising the compounds referred to. It will, however, also be understood that many detailed modifications are possible and, in particular, the scope of the invention is not to be construed as being limited solely by the illustrative example(s) or by the terms and expressions used herein merely in a descriptive or explanatory sense.

TABLE 1

In vitro activity (IC_{50} concentration in nM) of various compounds of Formula (I)



(I)

wherein

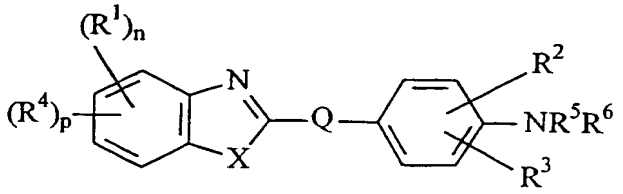
p = O, X = S, Q is a direct bond, R^3 = H, Y = O, R^7 = -CH(R^8)NH_3Cl

n	R^1	R^2	R^5	R^6	R^8	IC_{50} in MCF-7	IC_{50} in MDA468	Compound of formula
1	4-F	3-CH_3	H	H		<0.1	0.13	**Ia**
1	6-F	3-CH_3	H	H		<0.1	0.11	**Ib**
1	4-F	H	H	H		8.54	29.4	**Ic**
1	6-F	H	H	H		<0.1	48.1	**Id**
2	4,5-diF	3-CH_3	H	H		0.64	0.67	**Ie**
2	4,6-diF	3-CH_3	H	H		<0.1	5.35	**If**
2	5,7-diF	3-CH_3	H	H		0.9	4.4	**Ig**
1	7-F	3-CH_3	H	H		2.39	10.35	**Ih**
2	5,6-diF	3-CH_3	H	H		<0.1	3.55	**Ii**
1	5-F	3-CH_3	H	H		<0.1	<0.1	**Ik**
1	5-F	H	H	H		<0.1	<0.1	**Il**
1	4-F	3-I	H	H		7.88	9.11	**Im**
1	5-F	3-I	H	H		<0.1	<0.1	**In**
1	6-F	3-I	H	H		<0.1	<0.1	**Io**
1	4-F	3-Cl	H	H		0.95	1.93	**Ip**
1	5-F	3-Cl	H	H		7.09	18.9	**Iq**
1	6-F	3-Cl	H	H		4.08	11.7	**Ir**
1	4-F	3-Br	H	H		38.2	24	**Is**
1	5-F	3-Br	H	H		<0.1	0.2	**It**
1	6-F	3-Br	H	H		45.5	68.7	**Iu**
1	5-Br	3-CH_3	H	H		4.02		**Iaj**
1	5-I	3-CH_3	H	H		492.96	80.86*	**Iak**
1	7-I	3-CH_3	H	H		28.28	323.11	**Ial**
1	5-F	3-CH_3	H	$COCH_3$		7.64*	5.84*	**Iam**
1	5-F	3-CN	H	H		<0.1	<0.1	**Ian**
1	5-F	3-CH_2OH	H	H		<0.1	0.43	**Iaq**
0		3-F	H	H		1.58	33.41	
0		H	H	C(Y)R^7	CH_3	60	40	**Iv**
0		3-CH_3	H	C(Y)R^7	CH_3	360	340	**Iw**
0		3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	80	70	**Iz**
1	6-F	3-CH_3	H	C(Y)R^7	CH_3	44	297	**Iac**
1	5-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	40	158	**Iad**
1	6-F	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	147.31	328.09	**Iae**
1	5-F	3-CH_3	H	C(Y)R^7	CH_3	5.89	37.74	**Iaf**
2	5,6-diF	3-CH_3	H	C(Y)R^7	CH_3	33.06	216.9	**Iar**
2	5,6-diF	3-CH_3	H	C(Y)R^7	$(CH_2)_4NH_2$	30.69	301.87	**Ias**

* IC_{50} concentration in μM

CLAIMS

1. An arylbenzazole compound represented by the structural formula I below, or a pharmaceutically acceptable salt thereof,



(I)

wherein

X represents S or O;

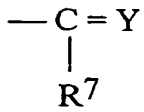
R^1 is selected from halogen, CF_3 and trimethyltin;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF_3;

R^3 represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R^4 represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R^5 and R^6 each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R^7 represents alkyl or $-CH(R^8)NH_2$ where R^8 represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, $-CH_2-$ or –CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

subject to the following provisos:

(a) alkyl or substituted alkyl groups are linear, branched or cyclic structures but when present as linear or branched structures in the

compound or as a moiety in another group such as alkoxy they are composed of less then ten carbon atoms;

(b) p represents zero or 1 when n represents 3;

(c) when n represents zero, R^5 or R^6 represents $-C(Y)-CH(R^8)NH_2$;

(d) where a group is optionally substituted, unless otherwise specified the or each substituent is selected from halogen, OH, SH, NH_2, COOH and $CONH_2$;

2. An arylbenzazole compound as claimed in Claim 1 further characterised by at least one of the following features:

(a) Alkyl groups when present as such or as a moiety in other groups such as alkoxy each contain less than six carbon atoms.

(b) at least some alkyl groups when present as such or as a moiety in other groups such as alkoxy are methyl or ethyl;

(c) halogen substitutents, when present, are selected from fluorine, iodine, bromine and chlorine.

3. An arylbenzazole compound as claimed in Claim 2 wherein there is a fluorine halogen substituent.

4. An arylbenzazole compound as claimed in Claim 3 wherein the compound incorporates the isotope ^{18}F.

5. An arylbenzazole compound as claimed in Claim 1 or 2 wherein R^1 is fluorine.

6. An arylbenzazole compound as claimed in any of the preceding claims wherein R^1 is in the 5-position of the benzazole moiety.

7. An arylbenzazole compound as claimed in any of the preceding claims wherein R^2 is a substitutent in the 3' position of the phenyl group.

8. An arylbenzazole compound as claimed in any of the preceding claims further characterised in that X is sulphur.

9. An arylbenzazole compound as claimed in any of the preceding claims wherein one of R^5 and R^6 is $C(Y)\text{-}CH(R^8)NH_2$ (or a salt thereof) as defined in Claim 1, and the other is hydrogen.

10. An arylbenzazole compound as claimed in any of the preceding claims further characterised in that Y is O and R^8 is selected from hydrogen, $-CH_3$, $-(CH_2)_4NH_2$ and $-CH_2OH$.

11. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, R^5 and R^6 are both hydrogen, and the combination of substituents R^3, X and R^2 is selected from one of the following combinations:

R^3	X	R^2
H	S	3'-Me
H	S	3'-Et
H	O	3'-I
H	S	3'-Br
H	S	3'-Cl
H	S	3'-CN
5'-Br	S	3'-Br
5'-Cl	S	3'-Cl
5'-Me	S	3'-Cl
H	S	3'-F

12. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, wherein R^3, R^5 and R^6 each represent H, wherein Q represents a direct bond and wherein n, R^1 and R^2 represent one of the following combinations:

N	R^1	R^2
1	4-F	3-CH_3
1	6-F	3-CH_3
1	4-F	H
1	6-F	H
2	4,5-diF	3-CH_3
2	4,6-diF	3-CH_3
2	5,7-diF	3-CH_3
1	7-F	3-CH_3
2	5,6-diF	3-CH_3
2	6,7-diF	3-CH_3
1	5-F	3-CH_3
1	5-F	H
1	4-F	3-I
1	5-F	3-I
1	6-F	3-I
1	4-F	3-Cl
1	5-F	3-Cl
1	6-F	3-Cl
1	4-F	3-Br
1	5-F	3-Br
1	6-F	3-Br

13. An arylbenzazole compound as claimed in Claim 1 or 2 wherein p = 0, X represents S, Q represents a direct bond, one of R^5 and R^6 represents H and the other represents $-C(O)CH(R^8)NH_2$, and wherein R^3 represents H, and n, R^1, R^2 and R^8 represent one of the following combinations.

N	R^1	R^2	R^8
Zero	-	H	$-CH_3$
Zero	-	3-CH_3	$-CH_3$
Zero	-	3-Cl	$-CH_3$
Zero	-	H	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-(CH_2)_4NH_2$
Zero	-	3-Cl	$-(CH_2)_4NH_2$
Zero	-	3-CH_3	$-CH_2OH$
1	6-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	$-(CH_2)_4NH_2$
1	6-F	3-CH_3	$-(CH_2)_4NH_2$
1	5-F	3-CH_3	$-CH_3$
1	5-F	3-CH_3	H

14. An arylbenzazole compound which is one of the following:

4-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4-Fluoro-2-(4'-aminophenyl)benzothiazole;

6-Fluoro-2-(4'-aminophenyl)benzothiazole;

4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-aminophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;

2-(4'-Aminophenyl)benzothiazole alanyl amide hydrochloride salt;

2-(4'-Amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

2-(4'-Amino-3'-chlorophenyl)benzothiazole alanyl amide hydrochloride salt;

2-(4'-Aminophenyl)benzothiazole lysyl amide dihydrochloride salt;

2-(4'-Amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;

2-(4'-Amino-3'-chlorophenyl)benzothiazole lysyl amide dihydrochloride salt;

2-(4'-Amino-3'-methylphenyl)benzothiazole serine hydrochloride salt;

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;

6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt;

5-Bromo-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;

5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt; and

5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole.

15. An arylbenzazole compound as claimed in any of the preceding claims for use in therapy as an active therapeutic substance characterised in that it is an acid addition salt derived from an acid selected from the group consisting of:

hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic and ethanesulphonic.

16. A compound as claimed in any one of Claims 1 to 15 for use in therapy.

17. A isotopically labelled arylbenzazole compound selected from the group consisting of 5-^{18}Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and 6-

18Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole.

18. A pharmaceutical formulation for medical use comprising, as the active compound, a compound as claimed in any one of Claims 1 to 17 together with a pharmaceutically acceptable carrier therefor.

19. A medical preparation containing a therapeutically effective non-toxic amount of a compound as claimed in any one of Claims 1 to 16 and a pharmaceutically inert excipient.

20. A pharmaceutical preparation in unit dosage unit form for administration to obtain a therapeutic effect as an antitumour agent in treating mammals, said preparation comprising, per dosage unit, a therapeutically-effective non-toxic amount of a compound as set forth in any one of Claims 1 to 16.

21. Use of a compound as claimed in any one of Claims 1 to 17 for the manufacture of a medical preparation for the treatment of tumours in mammals.

22. Use as claimed in Claim 21 wherein the medical preparation is for inhibiting the growth or proliferation of cancer cells.

23. A method of treating a mammal suffering from cancer so as to inhibit or reduce cancer cell growth, said method comprising administering to said mammal an effective amount of an antitumour composition wherein the active component is a benzazole compound as claimed in any one of Claims 1 to 16.

24. A method for the preparation of a compound as claimed in Claim 1 substantially as herein described with reference to Examples 1 to 45.

25. A method as claimed in Claim 24 wherein the compound is an amino acid amide prodrug which is prepared from the corresponding substituted benzothiazole by a method substantially as herein described under the heading "Route E".

FIGURE 1

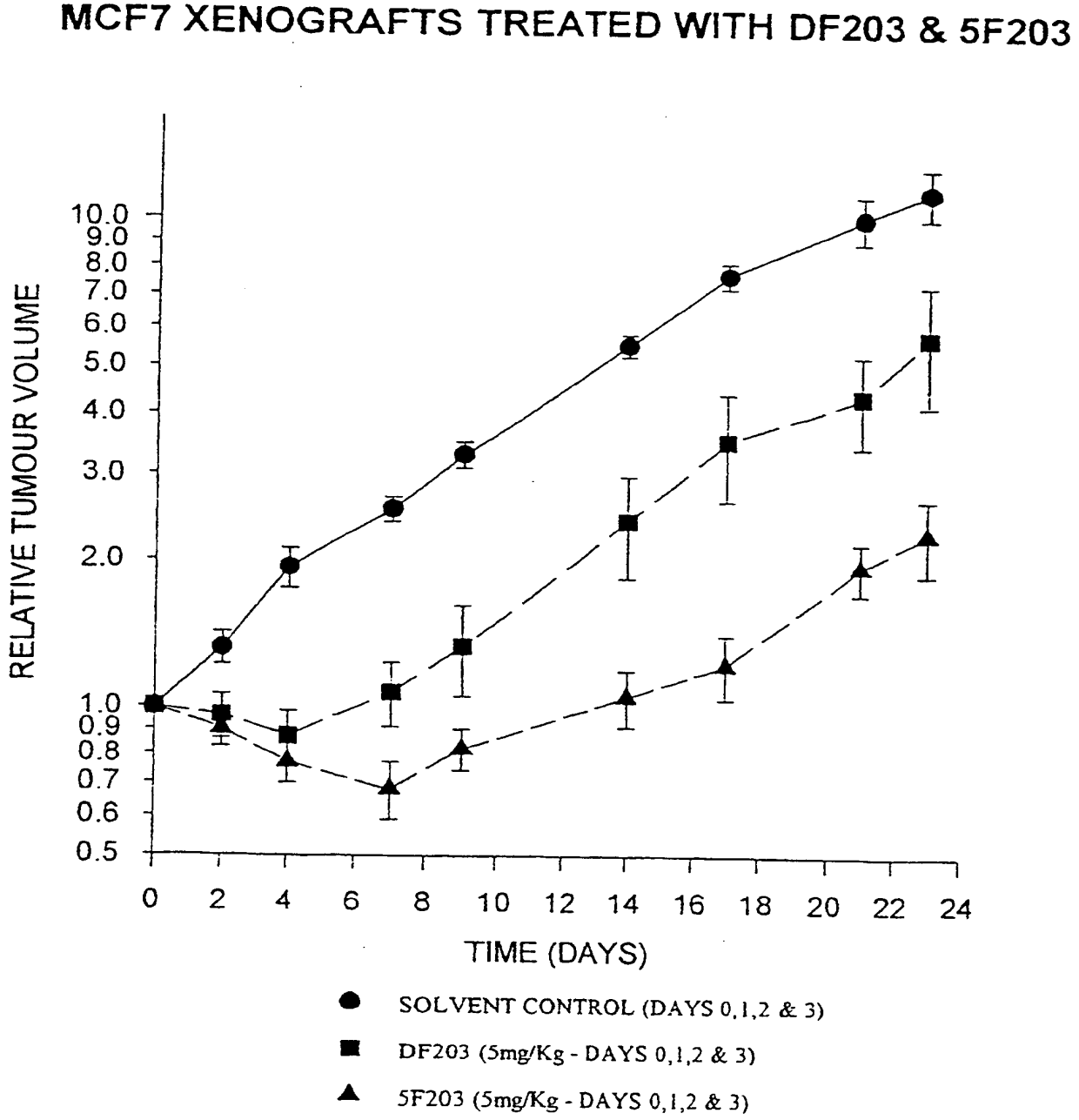
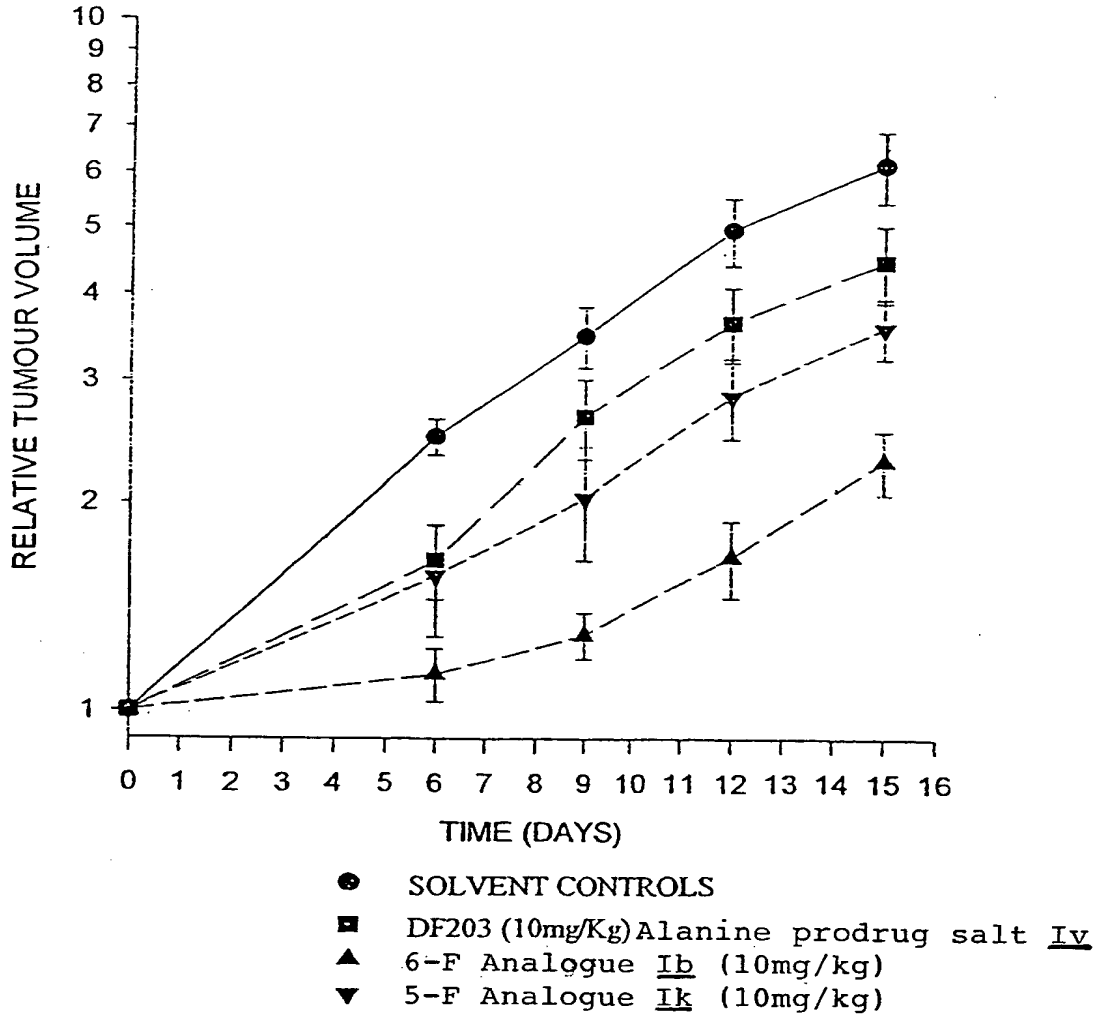

MCF7 XENOGRAFTS TREATED WITH DF203 & 5F203
RELATIVE TUMOUR VOLUME
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.9
0.8
0.7
0.6
0.5
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (DAYS)
SOLVENT CONTROL (DAYS 0,1,2 & 3)
DF203 (5mg/Kg - DAYS 0,1,2 & 3)
5F203 (5mg/Kg - DAYS 0,1,2 & 3)

FIGURE 2

COLO205 XENOGRAFTS TREATED WITH DF203 & ANALOGUES



INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/03210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/66 C07D277/64 C07D263/56 C07D263/57 C07F7/22
A61K31/428 A61K31/423 A61K31/555 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 06469 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 9 March 1995 (1995-03-09) cited in the application the whole document ---	1-25
X	WO 96 26932 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 6 September 1996 (1996-09-06) cited in the application the whole document ---	1-25
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2000	19/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 00/03210

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 22, no. 9, 10 May 1928 (1928-05-10) Columbus, Ohio, US; HAUSER H: "2-'Aminophenyl!benzothiazoles" page 1590; XP002154293 abstract & HELV. CHIM. ACTA, vol. 11, 1928, pages 198-209, ---	1,2,6,8
X	DE 23 33 378 A (BASF AG) 23 January 1975 (1975-01-23) the whole document, particularly page 7, examples 23 and 24 ---	1,2,6
X	DATABASE WPI Section Ch, Week 199919 Derwent Publications Ltd., London, GB; Class B02, AN 1999-226170 XP002154294 -& JP 11 060573 A (NIPPON KAYAKU KK), 2 March 1999 (1999-03-02) abstract ---	1-3,6,9
X	US 3 401 048 A (OKUBO I ET AL) 10 September 1968 (1968-09-10) the whole document, particularly example 4, starting material ---	1,2,6
X	US 3 257 204 A (SÜS O ET AL) 21 June 1966 (1966-06-21) the whole document ---	1,2,6,8
P,X	HUTCHINSON I ET AL: "The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles" TETRAHEDRON LETTERS, vol. 41, no. 3, January 2000 (2000-01), pages 425-428, XP004186279 ISSN: 0040-4039 the whole document -----	1-25

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 00 /03210

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11, 15, 16, 18-20 (all partly)

Present claims 1-11, 15, 16 and 18-20 relate to an extremely large number of possible compounds, their use and preparation. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and use claimed. In the present case, said claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty, in particular with regard to claims 1, 2, 6 and 8. So many documents were in fact retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) according to claim 1, wherein X is S, Q is a direct bond, R1 is halogen or trimethyltin, and n is 1, 2 or 3 (the other substituents being as indicated in claim 1), or wherein X is S, Q is a direct bond, and R5 and/or R6 is -C(Y)R7, (the other substituents being as indicated in claim 1), and the search report can only be considered as complete for the claims relating to said compounds, their use and preparation.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...nal Application No
PCT/GB 00/03210

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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